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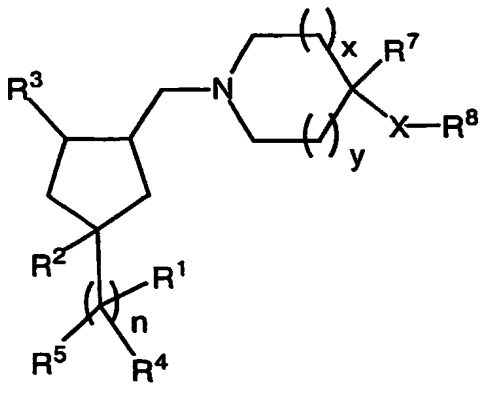
(54) Title: CYCLOPENTYL MODULATORS OF CHEMOKINE RECEPTOR ACTIVITY



(I)

(57) Abstract: The present invention is directed to compounds of formula (I) wherein R^1, R^2, R^3, R^4, R^5, R^7, R^8, X, n, x and y are defined herein which are useful as modulators of chemokine receptor activity. In particular, these compounds are useful as modulators of the chemokine receptors CCR-5 and/or CCR-3.

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TITLE OF THE INVENTION
CYCLOPENTYL MODULATORS OF CHEMOKINE RECEPTOR ACTIVITY

BACKGROUND OF THE INVENTION

Chemokines are chemotactic cytokines that are released by a wide variety of cells to attract macrophages, T cells, eosinophils, basophils and neutrophils to sites of inflammation (reviewed in Schall, Cytokine, 3, 165-183 (1991) and Murphy, Rev. Immun., 12, 593-633 (1994)). There are two classes of chemokines, C-X-C (α) and C-C (β), depending on whether the first two cysteines are separated by a single amino acid (C-X-C) or are adjacent (C-C). The α-chemokines, such as interleukin-8 (IL-8), neutrophil-activating protein-2 (NAP-2) and melanoma growth stimulatory activity protein (MGSA) are chemotactic primarily for neutrophils, whereas β-chemokines, such as RANTES, MIP-1α, MIP-1β, monocyte chemotactic protein-1 (MCP-1), MCP-2, MCP-3 and eotaxin are chemotactic for macrophages, T-cells, eosinophils and basophils (Deng, et al., Nature, 381, 661-666 (1996)).

The chemokines bind specific cell-surface receptors belonging to the family of G-protein-coupled seven-transmembrane-domain proteins (reviewed in Horuk, Trends Pharm. Sci., 15, 159-165 (1994)) which are termed "chemokine receptors." On binding their cognate ligands, chemokine receptors transduce an intracellular signal though the associated trimeric G protein, resulting in a rapid increase in intracellular calcium concentration. There are at least sixteen human chemokine receptors that bind or respond to β-chemokines with the following characteristic pattern: CCR-1 (or "CKR-1" or "CC-CKR-1") [MIP-1α, MIP-1β, MCP-3, RANTES] (Ben-Barruch, et al., J. Biol. Chem., 270, 22123-22128 (1995); Beote, et al, Cell, 72, 415-425 (1993)); CCR-2A and CCR-2B (or "CKR-2A"/"CKR-2A" or "CC-CKR-2A"/"CC-CKR-2A") [MCP-1, MCP-3, MCP-4]; CCR-3 (or "CKR-3" or "CC-CKR-3") [eotaxin, RANTES, MCP-3] (Combadiere, et al., J. Biol. Chem., 270, 16491-16494 (1995); CCR-4 (or "CKR-4" or "CC-CKR-4") [MIP-1α, RANTES, MCP-1] (Power, et al., J. Biol. Chem., 270, 19495-19500 (1995)); CCR-5 (or "CKR-5" or "CC-CKR-5") [MIP-1α, RANTES, MIP-1β] (Sanson, et al., Biochemistry, 35, 3362-3367 (1996)); and the Duffy blood-group antigen [RANTES, MCP-1] (Chaudhun, et al., J. Biol. Chem., 269, 7835-7838 (1994)). The β-chemokines include eotaxin, MIP ("macrophage inflammatory protein"), MCP ("monocyte chemoattractant protein") and RANTES ("regulation-upon-activation, normal T expressed and secreted").

Chemokine receptors, such as CCR-1, CCR-2, CCR-2A, CCR-2B, CCR-3, CCR-4, CCR-5, CXCR-3, CXCR-4, have been implicated as being important mediators of inflammatory and immunoregulatory disorders and diseases, including asthma, rhinitis and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. A review of the role of chemokines in allergic inflammation is provided by Kita, H., et al., J. Exp. Med. 183, 2421-2426 (1996). Accordingly, agents which modulate chemokine receptors would be useful in such disorders and diseases. Compounds which modulate chemokine receptors would be especially useful in the treatment and prevention of atopic conditions including allergic rhinitis, dermatitis, conjunctivitis, and particularly bronchial asthma.

A retrovirus designated human immunodeficiency virus (HIV-1) is the etiological agent of the complex disease that includes progressive destruction of the immune system (acquired immune deficiency syndrome; AIDS) and degeneration of the central and peripheral nervous system. This virus was previously known as LAV, HTLV-III, or ARV.

Certain compounds have been demonstrated to inhibit the replication of HIV, including soluble CD4 protein and synthetic derivatives (Smith, et al., Science, 238, 1704-1707 (1987)), dextran sulfate, the dyes Direct Yellow 50, Evans Blue, and certain azo dyes (U.S. Patent No. 5,468,469). Some of these antiviral agents have been shown to act by blocking the binding of gp120, the coat protein of HIV, to its target, the CD4 glycoprotein of the cell.

Entry of HIV-1 into a target cell requires cell-surface CD4 and additional host cell cofactors. Fusin has been identified as a cofactor required for infection with virus adapted for growth in transformed T-cells, however, fusin does not promote entry of macrophagetropic viruses which are believed to be the key pathogenic strains of HIV in vivo. It has recently been recognized that for efficient entry into target cells, human immunodeficiency viruses require a chemokine receptors, most probably CCR-5 or CXCR-4, as well as the primary receptor CD4 (Levy, N. Engl. J. Med., 335(20), 1528-1530 (Nov. 14 1996). The principal cofactor for entry mediated by the envelope glycoproteins of primary macrophage-trophic strains of HIV-1 is CCR5, a receptor for the β-chemokines RANTES, MIP-1α and MIP-1β (Deng, et al., Nature, 381, 661-666 (1996)). HIV attaches to the CD4 molecule on cells through a region of its envelope protein, gp120. It is believed that the CD-4 binding site on the gp120 of HIV interacts with the CD4 molecule on the cell surface, and undergoes conformational changes which allow it to bind to another

cell-surface receptor, such as CCR5 and/or CXCR-4. This brings the viral envelope closer to the cell surface and allows interaction between gp41 on the viral envelope and a fusion domain on the cell surface, fusion with the cell membrane, and entry of the viral core into the cell. It has been shown that β-chemokine ligands prevent HIV-1 from fusing with the cell (Dragic, et al., Nature, 381, 667-673 (1996)). It has further been demonstrated that a complex of gp120 and soluble CD4 interacts specifically with CCR-5 and inhibits the binding of the natural CCR-5 ligands MIP-1α and MIP-1β (Wu, et al., Nature, 384, 179-183 (1996); Trkola, et al., Nature, 384, 184-187 (1996)).

Humans who are homozygous for mutant CCR-5 receptors which do not serve as co-receptors for HIV-1 in vitro appear to be unusually resistant to HIV-1 infection and are not immuno-compromised by the presence of this genetic variant (Nature, 382, 722-725 (1996)). Absence of CCR-5 appears to confer substantial protection from HIV-1 infection (Nature, 382, 668-669 (1996)). Other chemokine receptors may be used by some strains of HIV-1 or may be favored by non-sexual routes of transmission. Although most HIV-1 isolates studied to date utilize CCR-5 or fusin, some can use both as well as the related CCR-2B and CCR-3 as co-receptors (Nature Medicine, 2(11), 1240-1243 (1996)). Nevertheless, drugs targeting chemokine receptors may not be unduly compromised by the genetic diversity of HIV-1 (Zhang, et al., Nature, 383, 768 (1996)). Accordingly, an agent which could block chemokine receptors in humans who possess normal chemokine receptors should prevent infection in healthy individuals and slow or halt viral progression in infected patients. By focusing on the host's cellular immune response to HIV infection, better therapies towards all subtypes of HIV may be provided. These results indicate that inhibition of chemokine receptors presents a viable method for the prevention or treatment of infection by HIV and the prevention or treatment of AIDS.

The peptides eotaxin, RANTES, MIP-1α, MIP-1β, MCP-1, and MCP-3 are known to bind to chemokine receptors. As noted above, the inhibitors of HIV-1 replication present in supernatants of CD8+ T cells have been characterized as the β-chemokines RANTES, MIP-1α and MIP-1β.

SUMMARY OF THE INVENTION

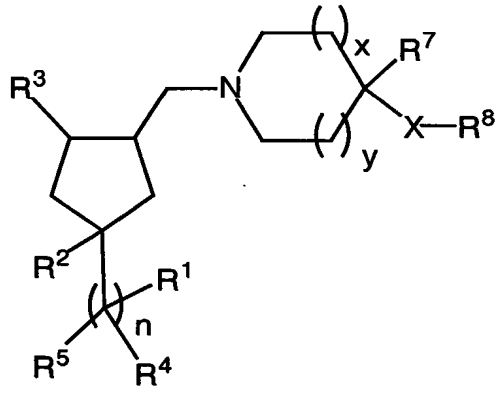
The present invention is directed to compounds which inhibit the entry of human immunodeficiency virus (HIV) into target cells and are of value in the prevention of infection by HIV, the treatment of infection by HIV and the prevention

and/or treatment of the resulting acquired immune deficiency syndrome (AIDS). The present invention also relates to pharmaceutical compositions containing the compounds and to a method of use of the present compounds and other agents for the prevention and treatment of AIDS and viral infection by HIV.

The present invention is further directed to compounds which are modulators of chemokine receptor activity and are useful in the prevention or treatment of certain inflammatory and immunoregulatory disorders and diseases, allergic diseases, atopic conditions including allergic rhinitis, dermatitis, conjunctivitis, and asthma, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. The invention is also directed to pharmaceutical compositions comprising these compounds and the use of these compounds and compositions in the prevention or treatment of such diseases in which chemokine receptors are involved.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to compounds of formula I:



I

wherein:

X is selected from: -(C_{0-6} alkyl)-Y-(C_{0-6} alkyl)-,
-(C_{0-6} alkyl)-C_{3-8} cycloalkyl-(C_{0-6} alkyl)-,
C_{2-10} alkenyl, and C_{2-10} alkynyl,
where the alkyl is unsubstituted or substituted with 1-7 substituents where the substituents are independently selected from:
(a) halo,
(b) hydroxy,
(c) -O-C_{1-3} alkyl, and
(d) trifluoromethyl,

and where Y is selected from:
a single bond, -O-, -SO_2-, -NR^{10}-, -NR^{10}-SO_2-, -SO_2-NR^{10}-,
-S-, and -SO-,

and where R^{10} is independently selected from: hydrogen, C_{1-6} alkyl, benzyl, phenyl, and C_{1-6} alkyl-C_{3-6} cycloalkyl,
which is unsubstituted or substituted with 1-3 substituents where the substituents are independently selected from: halo, C_{1-3} alkyl, C_{1-3} alkoxy and trifluoromethyl;

R^1 is selected from:

(1) $-CO_2H$,
(2) $-NO_2$,
(3) -tetrazolyl,
(4) -hydroxyisoxazole,
(5) $-SO_2NHCO-(C_{0-3}$ alkyl)$-R^9$, and
(6) $-P(O)(OH)_2$;

where R^9 is independently selected from: hydrogen, C_{1-10} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkyl-C_{3-6} cycloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, benzyl or phenyl, which is unsubstituted or substituted with 1-3 substituents where the substituents are independently selected from: halo, C_{1-3} alkyl, C_{1-3} alkoxy and trifluoromethyl,

R^2 is selected from:
(1) hydrogen, and
(2) hydroxy;

R^3 is selected from the group consisting of:
phenyl and heterocycle,
which is unsubstituted or substituted with 1-7 substituents where the substituents are independently selected from:
(a) halo,
(b) trifluoromethyl,
(c) hydroxy,
(d) C_{1-3} alkyl,
(e) $-O-C_{1-3}$ alkyl,
(f) $-CO_2R^9$,
(g) $-NR^9R^{10}$, and
(h) $-CONR^9R^{10}$;

R^4 and R^5 are independently selected from:
hydrogen, hydroxy, fluoro, C_{1-10} alkyl, C_{3-8} cycloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, phenyl, -(C_{1-6} alkyl)-phenyl, -(C_{1-6} alkyl)-C_{3-8} cycloalkyl, naphthyl, biphenyl, and heterocycle,

which is unsubstituted or substituted with 1-7 of R^{11} where R^{11} is independently selected from:

(a) halo,
(b) trifluoromethyl,
(c) hydroxy,
(d) C_{1-3} alkyl,
(e) -O-C_{1-3} alkyl,
(f) -CO_2R^9, and
(g) -$CONR^9R^{10}$,

or where R^4 and R^5 may be joined together to form a 3-8 membered saturated ring which may be unsubstituted or substituted with 1-7 of R^{11},
or where, if n is 1, R^2 and R^4 may be joined together to form a double bond;

R^7 is selected from:

(1) hydrogen,
(2) C_{1-6} alkyl, which is unsubstituted or substituted with 1-4 substituents where the substituents are independently selected from: hydroxy, cyano, and halo,
(3) hydroxy, and
(4) halo;

R^8 is selected from:

hydrogen, C_{3-8} cycloalkyl, phenyl, naphthyl, biphenyl, and heterocycle, which is unsubstituted or substituted with 1-7 of R^{12} where R^{12} is independently selected from:

(a) halo,
(b) cyano,
(c) hydroxy,
(d) C_{1-6} alkyl, which is unsubstituted or substituted with 1-5 of R^{13} where R^{13} is independently selected from: halo, cyano, hydroxy, C_{1-6} alkoxy, -CO_2H, -CO_2(C_{1-6} alkyl), trifluoromethyl, and -NR^9R^{10},
(e) -O-C_{1-6} alkyl, which is unsubstituted or substituted with 1-5 of R^{13},

(f) $-CF_3$,
(g) $-CHF_2$,
(h) $-CH_2F$,
(i) $-NO_2$,
(j) C_{0-6} alkyl-phenyl or C_{0-6} alkyl-heterocycle, which is unsubstituted or substituted with 1-7 substituents where the substituents are independently selected from:
  (i) halo,
  (ii) hydroxy,
  (iii) C_{1-6} alkyl,
  (iv) $-O-C_{1-6}$ alkyl,
  (v) $-CF_3$,
  (vi) $-OCF_3$,
  (vii) $-NO_2$,
  (viii) -CN,
  (ix) $-SO_2-C_{1-6}$ alkyl,
  (x) $-CO_2R^9$,
  (xi) $-NR^9R^{10}$,
  (xii) $-CONR^9R^{10}$,
  (xiii) $-SO_2-NR^9R^{10}$, and
  (xiv) $-NR^9-SO_2-R^{10}$;
(k) $-CO_2R^9$,
(l) tetrazolyl,
(m) $-NR^9R^{10}$,
(n) $-NR^9-COR^{10}$,
(o) $-NR^9-CO_2R^{10}$,
(p) $-CO-NR^9R^{10}$,
(q) $-OCO-NR^9R^{10}$,
(r) $-NR^9CO-NR^9R^{10}$,
(s) $-S(O)_m-R^9$, wherein m is an integer selected from 0, 1 and 2,
(t) $-S(O)_2-NR^9R^{10}$,
(u) $-NR^9S(O)_2-R^{10}$, and
(v) $-NR^9S(O)_2-NR^9R^{10}$;

n is an integer selected from 1, 2, 3 and 4;
x is an integer selected from 0, 1 and 2, and y is an integer selected from 0, 1 and 2, with the proviso that the sum of x and y is 2;

and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

One embodiment of the present invention is a compound of Formula I, wherein

R^1 is selected from:

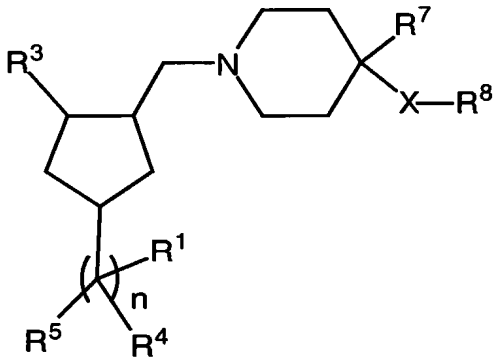
(1) $-CO_2H$,
(2) $-NO_2$,
(3) -tetrazolyl,
(4) -hydroxyisoxazole, and
(5) $-P(O)(OH)_2$;

each R^9 is independently selected from: hydrogen, C_{1-6} alkyl, C_{5-6} cycloalkyl, benzyl or phenyl, which is unsubstituted or substituted with 1-3 substituents where the substituents are independently selected from: halo, C_{1-3} alkyl, C_{1-3} alkoxy and trifluoromethyl;

and all other variables are as previously defined;

and pharmaceutically acceptable salts thereof and individual diastereomers thereof

Preferred compounds of the present invention include those of formula Ia:

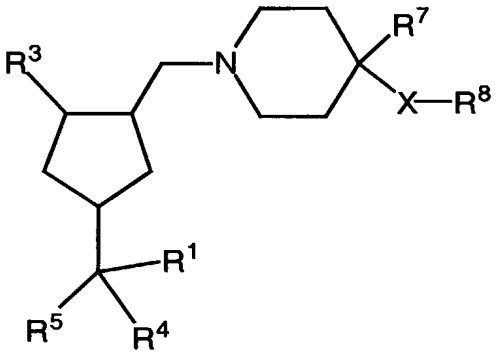


Ia

wherein R^1, R^3, R^4, R^5, R^7, R^8, X and n are defined herein;

and pharmaceutically acceptable salts and individual diastereomers thereof.

More preferred compounds of the present invention include those of formula Ic:

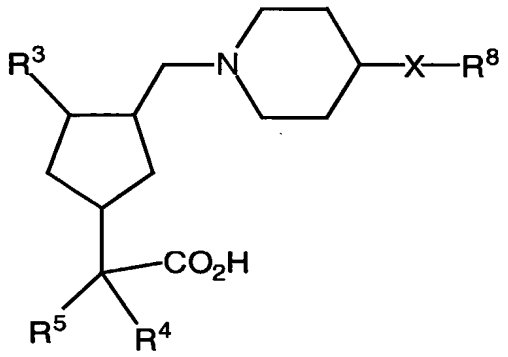


Ic

wherein R^1, R^3, R^4, R^5, R^7, R^8 and X are defined herein;

and pharmaceutically acceptable salts and individual diastereomers thereof.

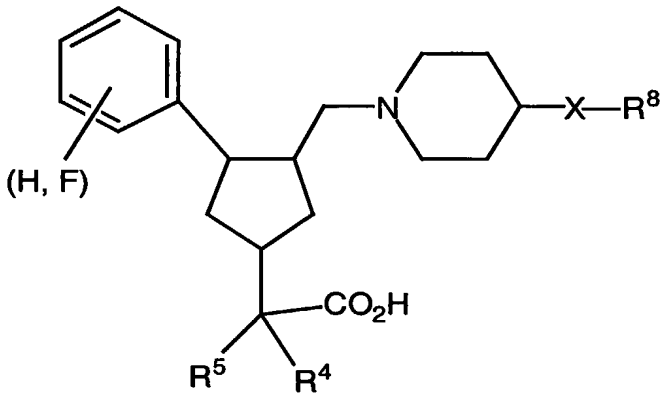
Highly preferred compounds of the present invention include those of formula Id:



Id

wherein R^3, R^4, R^5, R^8 and X are defined herein;
and pharmaceutically acceptable salts and individual diastereomers thereof.

More highly preferred compounds of the present invention include those of formula Ie:



Ie

wherein R^4, R^5, R^8 and X are defined herein;
and pharmaceutically acceptable salts and individual diastereomers thereof.

In the present invention it is preferred that R^1 is selected from:

(1) $-CO_2H$,
(2) $-P(O)(OH)_2$, and
(3) -tetrazolyl.

In the present invention it is more preferred that R^1 is selected from:

(1) $-CO_2H$, and

(2) -tetrazolyl.

In the present invention it is even more preferred that R^1 is $-CO_2H$.

In the present invention it is preferred that R^3 is selected from the group consisting of:

phenyl and thienyl,

which may be unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from:

(a) halo,
(b) trifluoromethyl,
(c) hydroxy,
(d) C_{1-3} alkyl, and
(e) $-O-C_{1-3}$ alkyl.

In the present invention it is more preferred that R^3 is selected from the group consisting of:

phenyl and thienyl,

which may be unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from:

(a) fluoro,
(b) chloro,
(c) trifluoromethyl,
(d) hydroxy, and
(e) C_{1-3} alkyl.

In the present invention it is even more preferred that R^3 is selected from the group consisting of:

phenyl, which may be unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from:

(a) fluoro, and
(b) chloro; and

unsubstituted thienyl.

In the present invention it is still more preferred that R^3 is unsubstituted phenyl, (3-fluoro)phenyl or 3-thienyl.

In the present invention it is preferred that R^2 is hydrogen.

In the present invention it is preferred that R^4 is hydrogen or C_{1-6} alkyl.

In the present invention it is more preferred that R^4 is hydrogen or methyl.

In the present invention it is preferred that R^5 is selected from: hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{1-6} alkyl-C_{3-8} cycloalkyl, and phenyl.

In the present invention it is more preferred that R^5 is selected from: hydrogen, methyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, cyclohexyl, -CH_2-cyclopropyl, -CH_2-cyclobutyl and phenyl.

In the present invention it is preferred that R^4 and R^5 are joined together to form a C_{3-8} cycloalkyl ring.

In the present invention it is also preferred that R^4 and R^2 are joined together to form a double bond.

In the present invention it is more preferred that R^4 and R^2 are joined together to form a Z-double bond.

In the present invention it is preferred that R^7 is hydrogen, fluoro, hydroxy or C_{1-6} alkyl.

In the present invention it is more preferred that R^7 is hydrogen or fluoro.

In the present invention it is even more preferred that R^7 is hydrogen.

In the present invention it is preferred that X is:
-(C_{0-4} alkyl)-Y-(C_{0-4} alkyl)-,
where the alkyl is unsubstituted or substituted with 1-4 substituents where the substituents are independently selected from:
(a) halo,
(b) hydroxy,
(c) -O-C_{1-3} alkyl, and
(d) trifluoromethyl,
and where Y is selected from:
a single bond, -O-, -SO_2-, -NR^{10}-, -S-, and -SO-,
and where R^{10} is independently selected from: hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, benzyl, phenyl, and C_{1-6} alkyl-C_{3-6} cycloalkyl, which is unsubstituted or substituted with 1-3 substituents where the substituents are independently selected from: halo, C_{1-3} alkyl, C_{1-3} alkoxy and trifluoromethyl.

In the present invention it is more preferred that X is:
-(C_{0-2} alkyl)-Y-(C_{0-2} alkyl)-,
where the alkyl is unsubstituted or substituted with 1-4 substituents where the substituents are independently selected from:
(a) halo,
(b) hydroxy,
(c) -O-C_{1-3} alkyl, and
(d) trifluoromethyl,
and where Y is selected from:
a single bond, -O-, -SO_2-, -NR^{10}-, -S-, and -SO-,
where R^{10} is independently selected from: hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, benzyl, phenyl, and C_{1-6} alkyl-C_{3-6} cycloalkyl, which is unsubstituted or substituted with 1-3 substituents where the substituents are independently selected from: halo, C_{1-3} alkyl, C_{1-3} alkoxy and trifluoromethyl.

In the present invention it is even more preferred that X is selected from:

-(C_{0-2} alkyl)-Y-(C_{0-2} alkyl)-, where the alkyl is unsubstituted or substituted with fluoro,

and where Y is selected from:

a single bond, $-SO_2-$, -SO-, and $-NR^{10}-$,

where R^{10} is independently selected from: hydrogen, C_{1-3} alkyl, C_{2-3} alkenyl, and C_{2-3} alkynyl.

In the present invention it is still more preferred that X is selected from:

(1) a single bond,
(2) $-CH_2CH_2-$,
(3) $-CH_2CH_2CH_2-$,
(4) $-CH_2CH_2-CF_2-$,
(5) $-CH_2CH_2-SO_2-$, and
(6) $-CH_2CH_2-SO-$.

In the present invention it is preferred that R^8 is selected from: phenyl, naphthyl, cyclohexyl, benzoimidazolyl, benzofurazanyl, imidazopyridyl, imidazolyl, isoxazolyl, oxazolyl, pyrazinyl, pyridazinyl, pyridyl, pyrimidyl, thiazolyl tetrazolopyridyl, pyrazolyl, tetrahydroindazolyl, tetrahydroimidazopyridyl, and tetrahydropyrazolopyridyl;

which is unsubstituted or substituted with 1-7 substituents where the substituents are independently selected from:

(a) halo,
(b) cyano,
(c) hydroxy,
(d) C_{1-6} alkyl, which is unsubstituted or substituted with 1-5 of R^{13} where R^{13} is independently selected from: halo, cyano, hydroxy, C_{1-6} alkoxy, $-CO_2H$, $-CO_2(C_{1-6}$ alkyl), trifluoromethyl, and $-NR^9R^{10}$, wherein R^9 and R^{10} are independently selected from: hydrogen, C_{1-6} alkyl, C_{5-6} cycloalkyl, benzyl or phenyl, which is unsubstituted or

substituted with 1-3 substituents where the substituents are independently selected from: halo, C_{1-3} alkyl, C_{1-3} alkoxy and trifluoromethyl;

(e) -O-C_{1-6} alkyl, which is unsubstituted or substituted with 1-5 of R^{13},

(f) $-CF_3$,

(g) $-CHF_2$,

(h) $-CH_2F$,

(i) $-NO_2$,

(j) C_{0-6} alkyl-phenyl or C_{0-6} alkyl-heterocycle, which is unsubstituted or substituted with 1-7 substituents where the substituents are independently selected from:

(i) halo,

(ii) hydroxy,

(iii) C_{1-6} alkyl,

(iv) -O-C_{1-6} alkyl,

(v) $-CF_3$,

(vi) $-OCF_3$,

(vii) $-NO_2$,

(viii) -CN,

(ix) $-SO_2$-C_{1-6} alkyl,

(x) $-CO_2R^9$,

(xi) $-NR^9R^{10}$,

(xii) $-CONR^9R^{10}$,

(xiii) $-SO_2$-NR^9R^{10}, and

(xiv) $-NR^9$-SO_2-R^{10};

(k) $-CO_2R^9$,

(l) tetrazolyl,

(m) $-NR^9R^{10}$,

(n) $-NR^9$-COR^{10},

(o) $-NR^9$-CO_2R^{10},

(p) -CO-NR^9R^{10},

(q) -OCO-NR^9R^{10},

(r) $-NR^9CO$-NR^9R^{10},

(s) $-S(O)_m$-R^9,wherein m is an integer selected from 0, 1 and 2,

(t) $-S(O)_2-NR^9R^{10}$,
(u) $-NR^9S(O)_2-R^{10}$, and
(v) $-NR^9S(O)_2-NR^9R^{10}$.

In an aspect of the preceding embodiment, in the present invention it is preferred that R^8 is selected from: phenyl, naphthyl, cyclohexyl, benzoimidazolyl, benzofurazanyl, imidazopyridyl, imidazolyl, isoxazolyl, oxazolyl, pyrazinyl, pyridazinyl, pyridyl, pyrimidyl, thiazolyl, and tetrazolopyridyl; which is unsubstituted or substituted with 1-7 substituents as set forth in the preceding paragraph.

In the present invention it is more preferred that R^8 is selected from: phenyl, imidazopyridyl, imidazolyl, oxazolyl, pyrazolyl, pyridyl, thiazolyl, tetrahydroindazolyl, tetrahydroimidazopyridyl, and tetrahydropyrazolopyridyl;

which is unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from:

(a) halo,
(b) cyano,
(c) $-NO_2$,
(d) $-CF_3$,
(e) $-CHF_2$,
(f) $-CH_2F$,
(h) C_{1-6} alkyl,
(i) C_{1-3} alkyl-phenyl or C_{1-3} alkyl-pyridyl, which is unsubstituted or substituted with 1-4 substituents where the substituents are independently selected from:
  (i) halo,
  (ii) C_{1-6} alkyl,
  (iii) $-O-C_{1-6}$ alkyl,
  (iv) $-CF_3$,
  (vi) $-OCF_3$,
  (vii) -CN, and
(j) $-O-C_{1-6}$ alkyl.

In an aspect of the preceding embodiment, in the present invention it is preferred that R^8 is selected from: phenyl, imidazopyridyl, imidazolyl, oxazolyl, pyrazolyl, pyridyl, and thiazolyl; which is unsubstituted or substituted with 1-5 substituents as set forth in the preceding paragraph.

In the present invention it is even more preferred that R^8 is selected from: imidazolyl, oxazolyl, pyrazolyl, thiazolyl, tetrahydroindazolyl, tetrahydroimidazopyridyl, and tetrahydropyrazolopyridyl;
which is unsubstituted or substituted with 1-3 substituents where the substituents are independently selected from:

(a) fluoro,
(b) cyano,
(c) C_{1-3} alkyl,
(d) $-CH_2$-phenyl, which is unsubstituted or substituted with 1-4 substituents where the substituents are independently selected from:
  (i) fluoro,
  (ii) chloro,
  (iii) $-O-CH_3$,
  (iv) $-CF_3$,
  (v) -CN, and
(e) $-CF_3$.

In an aspect of the preceding embodiment, in the present invention it is preferred that R^8 is selected from: imidazolyl, oxazolyl, pyrazolyl, and thiazolyl; which is unsubstituted or substituted with 1-3 substituents as set forth in the preceding paragraph.

In the present invention it is still more preferred that R^8 is selected from: 5-(3-benzyl)pyrazolyl, 5-(1-methyl-3-benzyl)pyrazolyl, 5-(1-ethyl-3-benzyl)pyrazolyl, 5-(2-benzyl)thiazolyl, 5-(2-benzyl-4-methyl)thiazolyl, and 5-(2-benzyl-4-ethyl)thiazolyl).

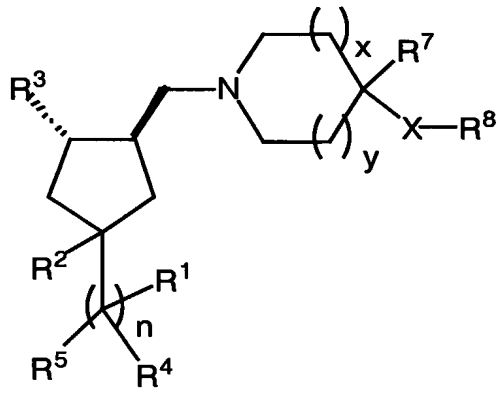
In the present invention it is preferred that n is an integer selected from 1, 2 and 3.

In the present invention it is more preferred that n is an integer which is 1 or 2.

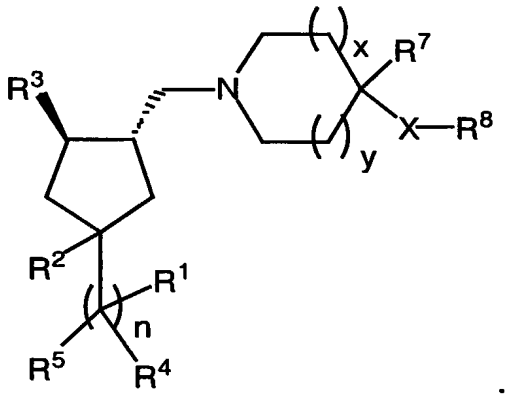
In the present invention it is preferred that x is an integer which is 1 and y is an integer which is 1.

It is to be understood that embodiments of the present invention include, but are not limited to, compounds of formula I wherein R^1, R^2, R^3, R^4, R^5, R^7, R^8, X, n, x and y are defined in accordance with one of the embodiments or aspects thereof as set forth above. Any and all possible combinations of preferred, more preferred, even more preferred, highly preferred, more highly preferred, and most preferred definitions of these variables in formulas I are within the scope of the present invention.

The compounds of the instant invention have at least two asymmetric centers at the ring junction of the substitutents bearing the piperidine and R^3. Additional asymmetric centers may be present depending upon the nature of the various substituents on the molecule. Each such asymmetric center will independently produce two optical isomers and it is intended that all of the possible optical isomers and diastereomers in mixtures and as pure or partially purified compounds are included within the ambit of this invention. The relative configurations of the more preferred compounds of this invention are of the trans orientation, i.e. as depicted:



or



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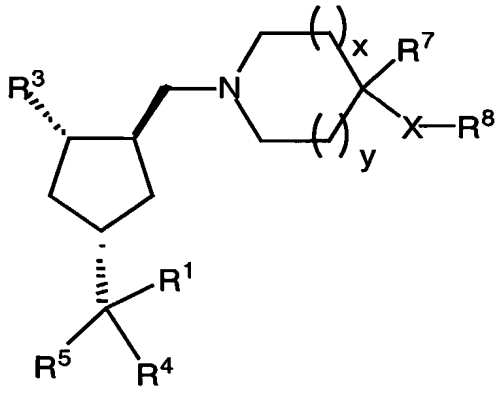
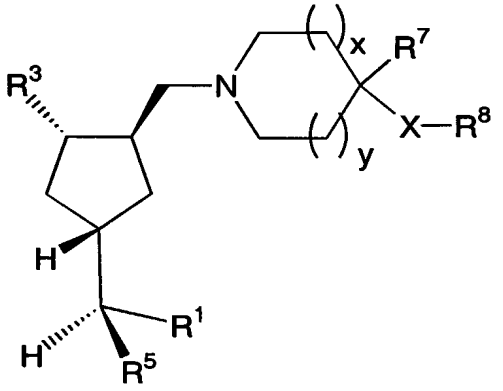
The relative configurations of the even more preferred compounds of this invention with respect to the configuration at the 1-position of the cyclopentane ring is 1,3-trans of the orientation as depicted:



The relative configurations of the most preferred compounds of this invention with respect to the configuration at the 1-position of the cyclopentane ring is 1,3-trans and with the (S)-stereochemistry at the 1,1'-position of the orientation as depicted:



The independent syntheses of these diastereomers or their chromatographic separations may be achieved as known in the art by appropriate modification of the methodology disclosed herein. Their absolute stereochemistry may be determined by the x-ray crystallography of crystalline products or crystalline intermediates which are derivatized, if necessary, with a reagent containing an asymmetric center of known absolute configuration.

As appreciated by those of skill in the art, halo or halogen as used herein are intended to include chloro, fluoro, bromo and iodo. Similarly, C_{1-8}, as in C_{1-8} alkyl is defined to identify the group as having 1, 2, 3, 4, 5, 6, 7 or 8 carbons in a linear or branched arrangement, such that C_{1-8} alkyl specifically includes methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl and octyl. Likewise, C_0, as in C_0 alkyl is defined to identify the presence of a direct covalent bond.

The term "heterocycle" (which may alternatively be referred to as "heterocyclic") refers to a 4- to 8-membered monocyclic ring, a 7- to 11-membered bicyclic system, or a 10 to 15-membered tricyclic ring system, any ring of which is saturated or unsaturated (partially or totally), and which consists of carbon atoms and one or more heteroatoms (e.g., from 1 to 4 heteroatoms) selected from N, O and S, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, the nitrogen heteroatom may optionally be quaternized, and a ring carbon may optionally be oxidized (i.e., is substituted with oxo). The heterocyclic ring may be attached at any heteroatom or carbon atom, provided that attachment results in the creation of a stable structure. A preferred heterocycle is a 4- to 8-membered monocyclic ring or a 7- to 11-membered bicyclic system, as defined and described above.

The term "heterocycle" as used herein is intended to include the following groups: benzoimidazolyl, benzofuranyl, benzofurazanyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, indolazinyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthpyridinyl, oxadiazolyl, oxazolyl, oxetanyl, pyranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridopyridinyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, tetrahydropyranyl, tetrazolyl, tetrazolopyridyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, azetidinyl, 1,4-dioxanyl, hexahydroazepinyl, piperazinyl, piperidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, dihydrobenzoimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidinyl, methylenedioxybenzoyl, tetrahydrofuranyl, and tetrahydrothienyl, and N-oxides thereof.

The term "heterocycle" as used herein is also intended to include, but is not limited to, the following groups: methylenedioxyphenyl, imidazopyridyl, imidazopyrimidinyl, imidazopyridazinyl, imidazopyrazinyl, imidazotriazinyl, imidazothiopheyl, pyrazolopyridyl, pyrazolopyrimidinyl, pyrazolopyridazinyl, pyrazolopyrazinyl, pyrazolotriazinyl, pyrazolothiophenyl, triazolopyridyl, triazolopyrimidinyl, triazolopyridazinyl, triazolopyrazinyl, triazolothiophenyl, tetrahydroimidazopyridinyl, tetrahydropyrazolopyridinyl, tetrahydrotriazopyridinyl, tetrahydrotriazolopyridazinyl, and tetrahydroindazolyl.

The term "heterocycle" as used herein is also intended to include, but is not limited to, the following groups: tetrahydroimidazopyrimidyl, tetrahydroimidazopyrazinyl, tetrahydroimidazopyridazinyl, tetrahydrotriazolopyrimidyl, tetrahydrotriazolopyrazinyl, tetrahydropyrazolopyrimidyl, tetrahydropyrazolopyrazinyl, imidazothiazolyl, and imidazothiadiazolyl.

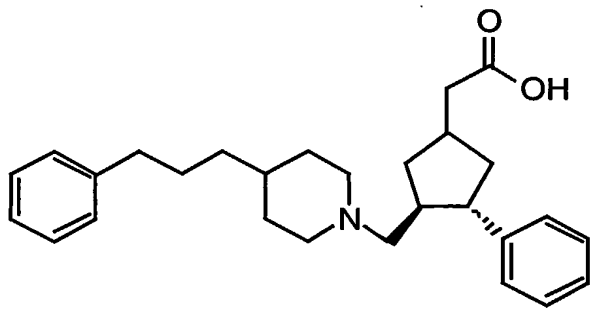
The term "heterocycle" as used herein is also intended to include, but is not limited to, oxopyridinyl (e.g., 2-oxopyridinyl), oxopiperidinyl, and oxopyrazolyl.

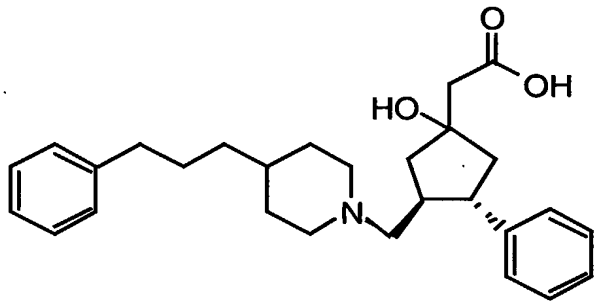
The terms "thiophenyl" and "thienyl" have the same meaning herein and are used interchangeably. Similarly, the following pairs of terms are used interchangeably: "indazolyl" and "benzopyrazolyl"; "pyridinyl" and "pyridyl".

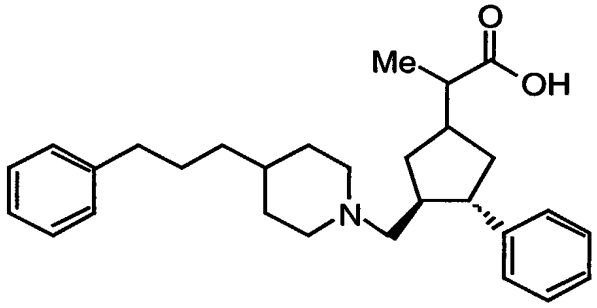
In the expression "... which is unsubstituted or substituted with ... ", "which" is intended to refer back to all preceding chemical groups in the particular definition in which the expression appears, unless a contrary meaning is expressed or is implied by the context. Furthermore, the term "substituted" in the expression includes mono- and poly-substitution by a named substituent to the extent such single and multiple substitution is chemically allowed in any of the named chemical groups. Thus, for example, the expression "is independently selected from: hydrogen, C_{1-6} alkyl, C_{5-6} cycloalkyl, benzyl or phenyl, which is unsubstituted or substituted with 1-3 substituents ...", encompasses hydrogen, C_{1-6} alkyl, C_{5-6} cycloalkyl, benzyl, phenyl, mono- and di- and tri-substituted C_{1-6} alkyl, mono- and di- and tri-substituted C_{5-6} cycloalkyl, mono- and di- and tri-substituted benzyl and mono- and di- and tri-substituted phenyl.

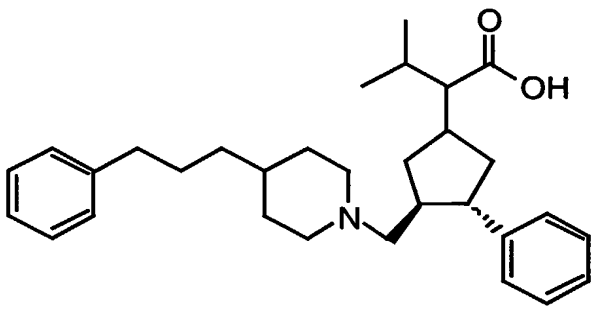
Exemplifying the invention is the use of the compounds disclosed in the Examples and herein.

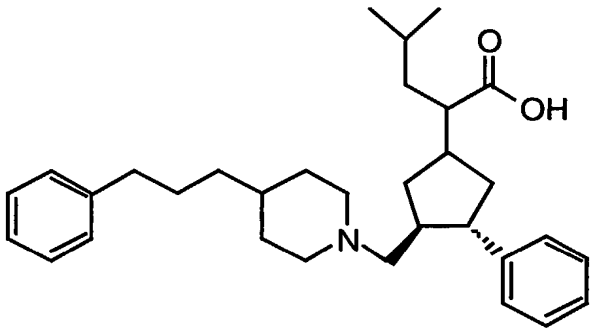
Specific compounds within the present invention include a compound which is selected from the group consisting of:

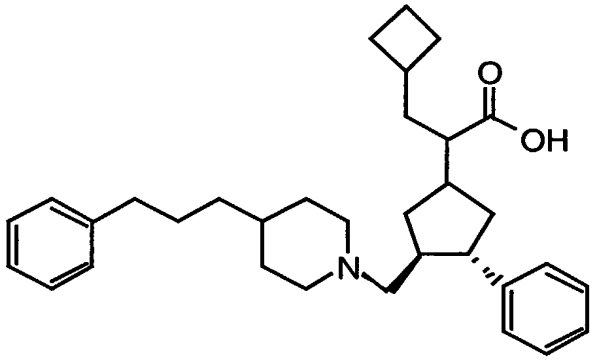


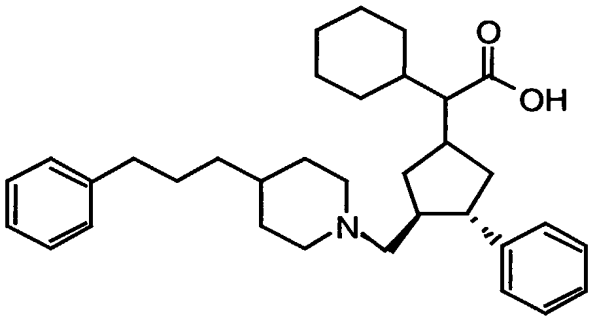












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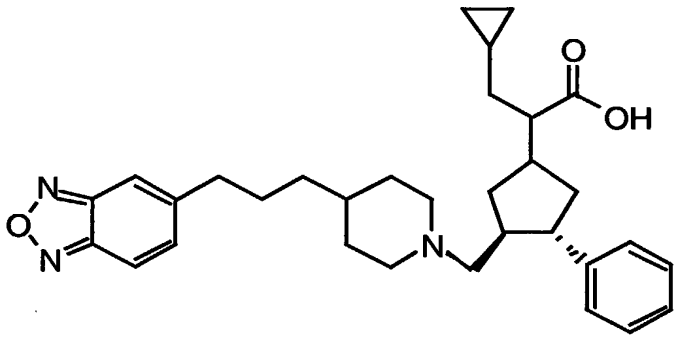

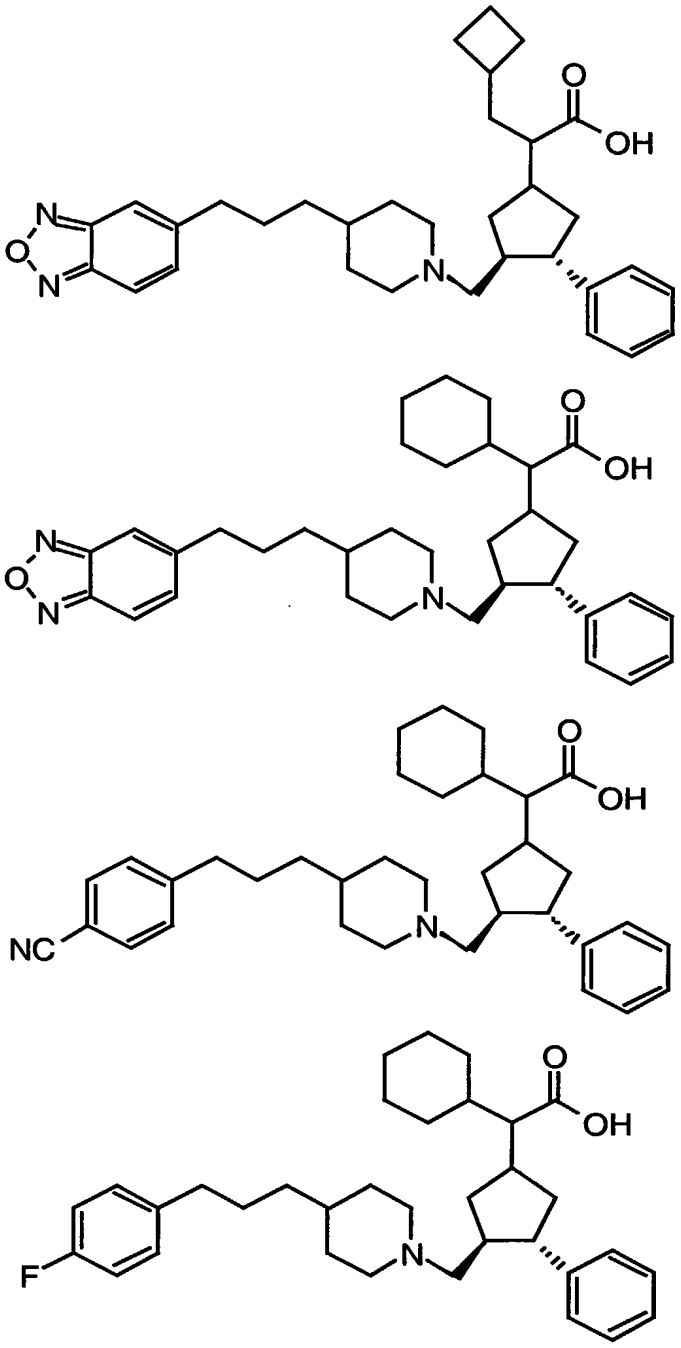

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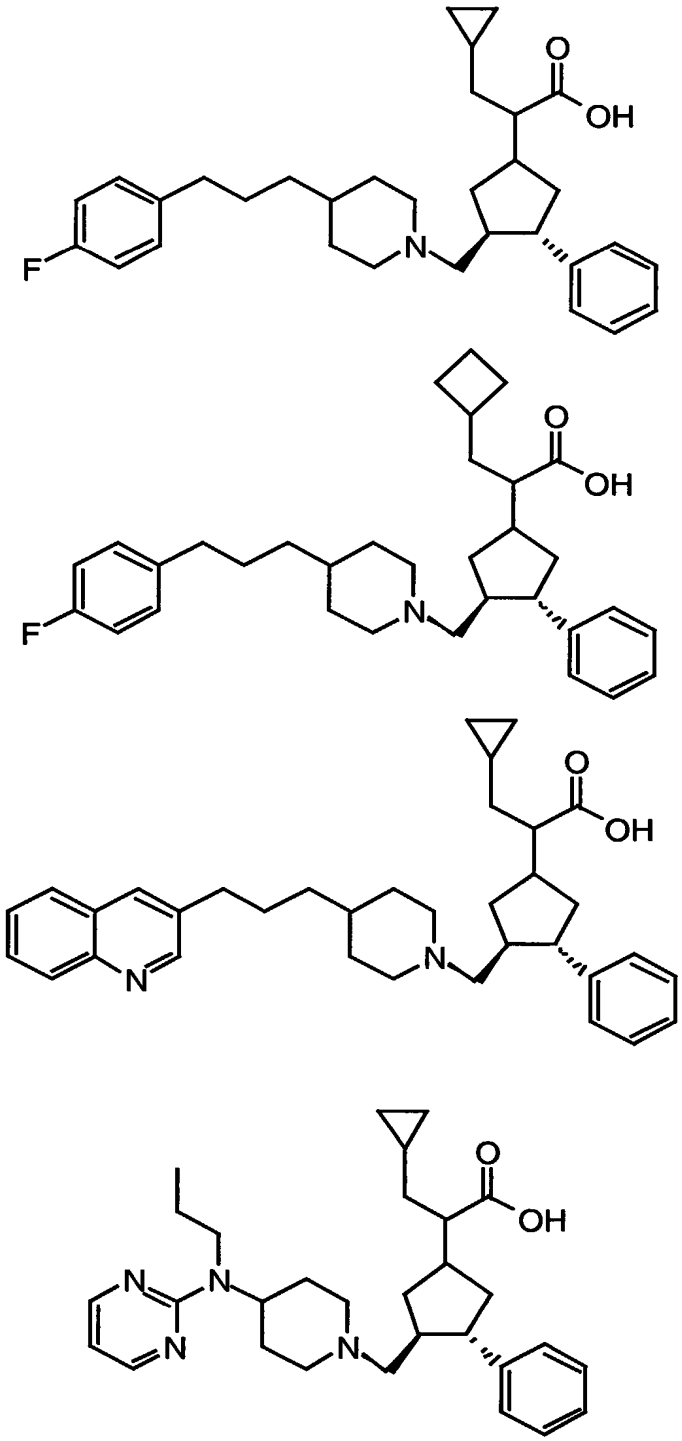

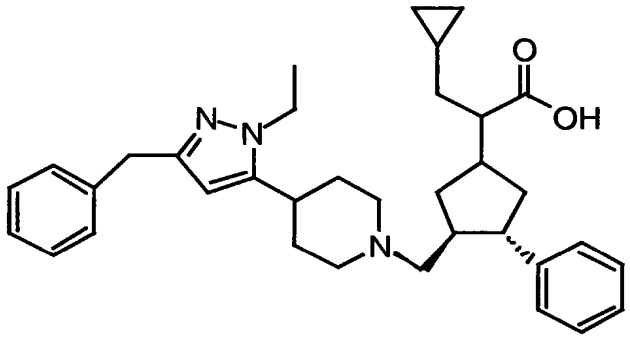

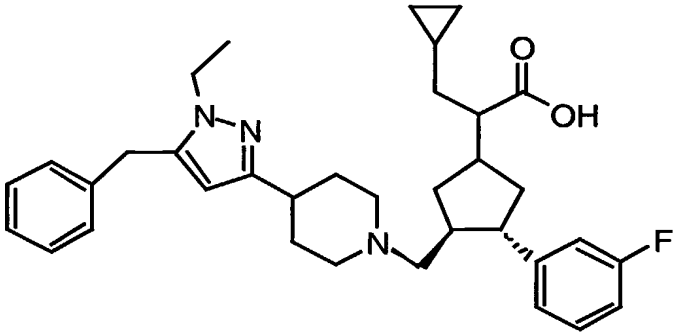

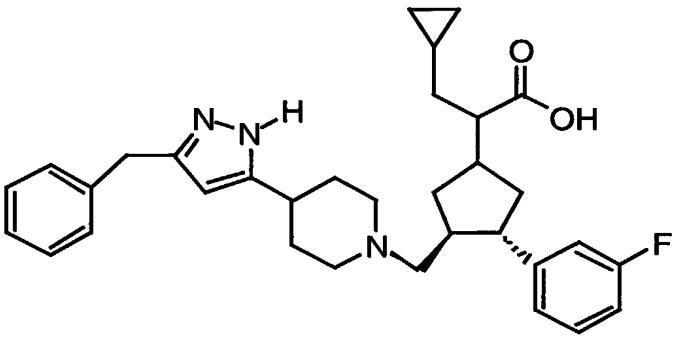

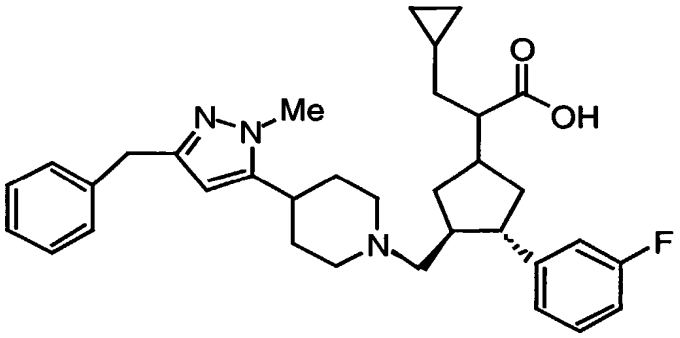

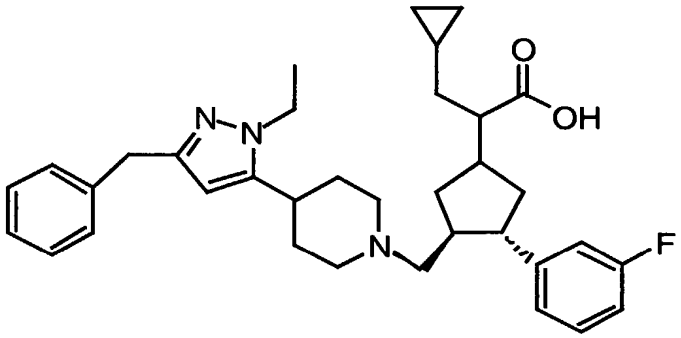

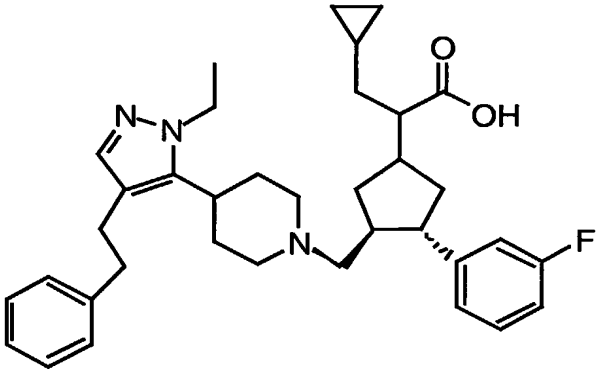

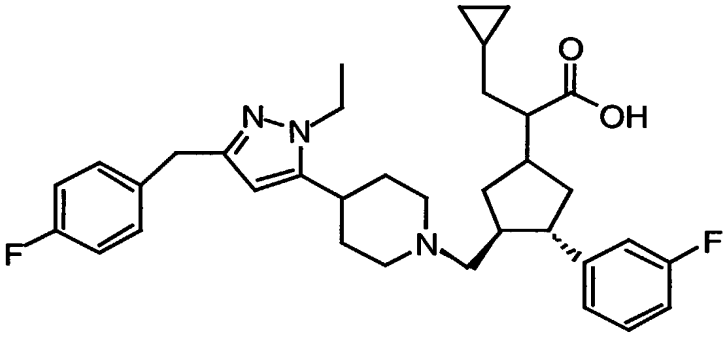

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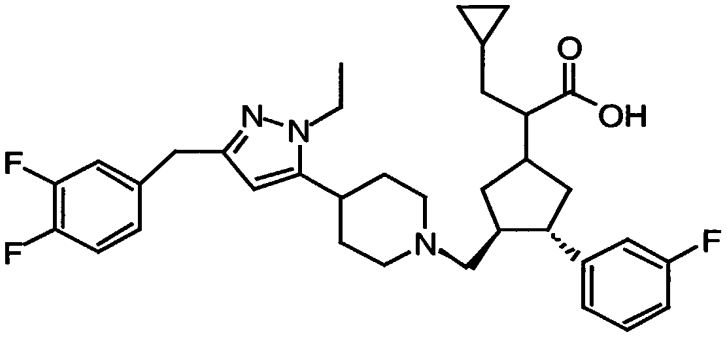
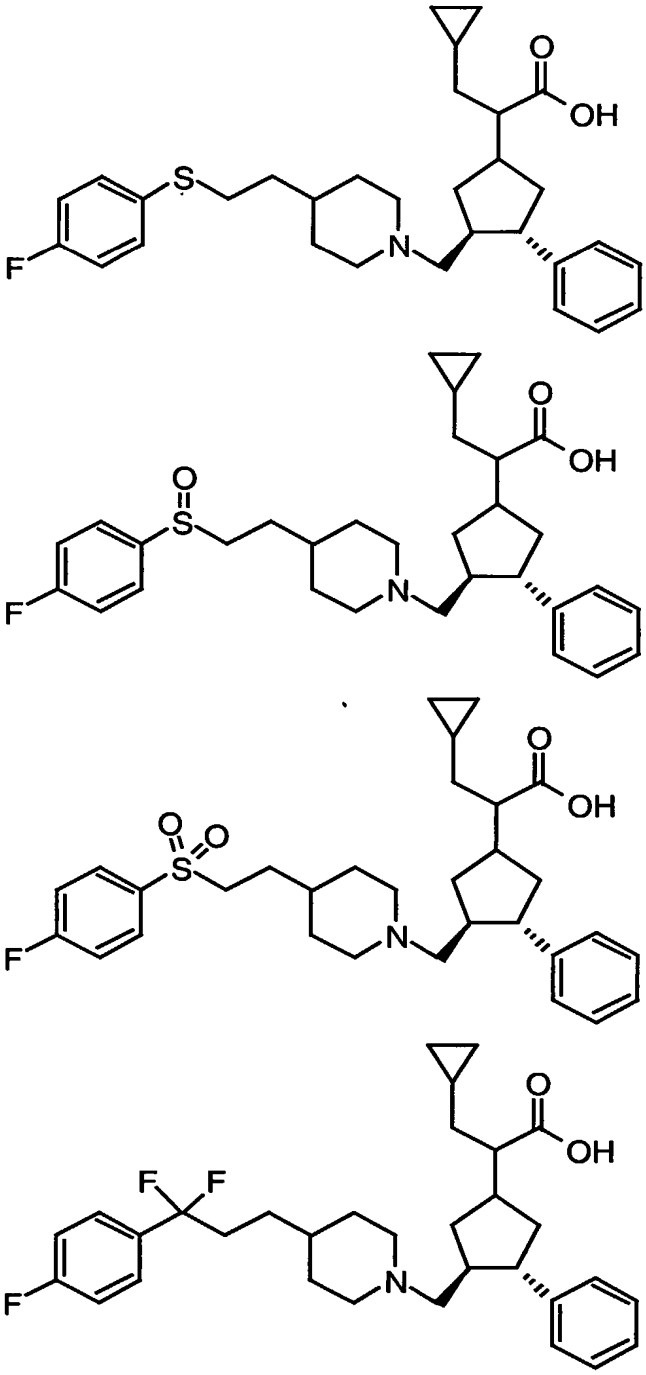
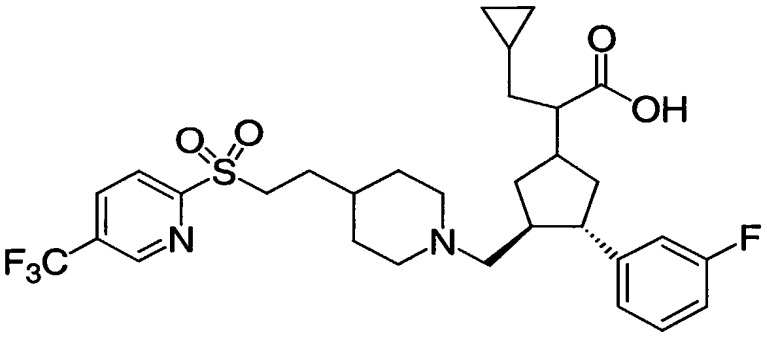
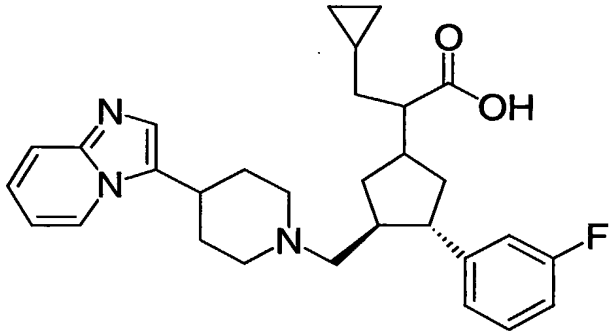


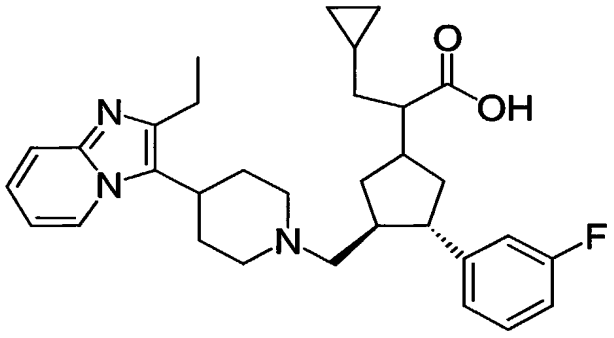


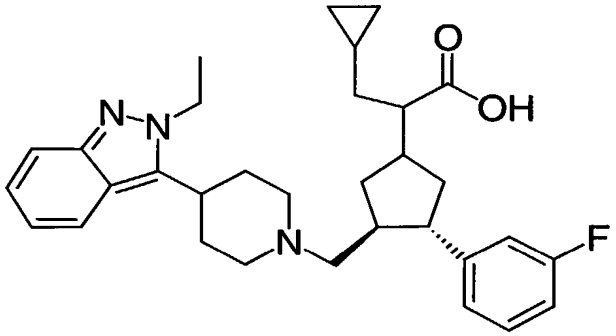
and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

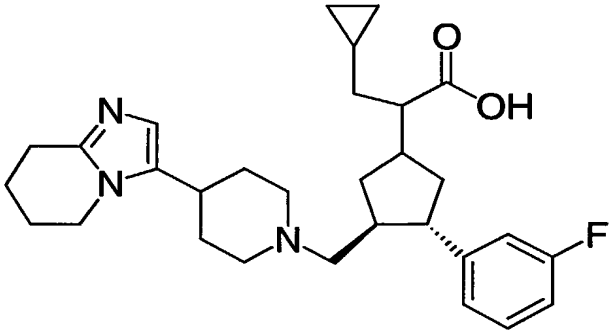
Specific compounds within the present invention also include compounds selected from the group consisting of:

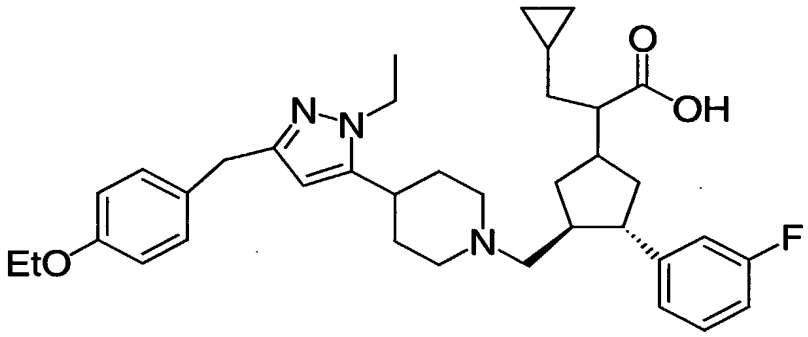












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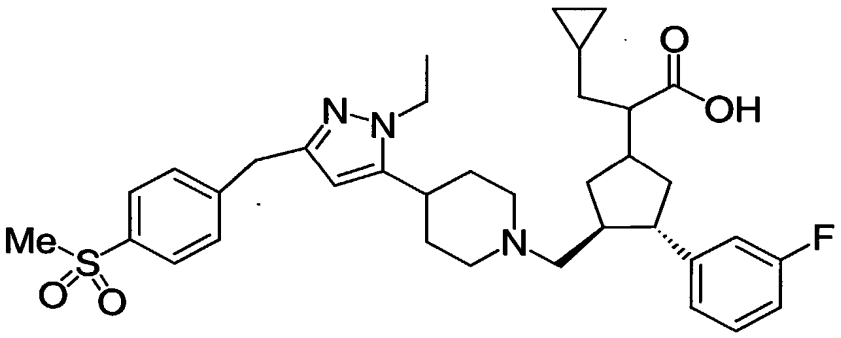

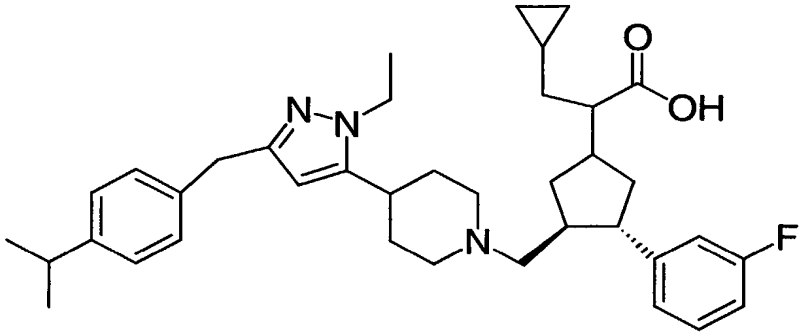

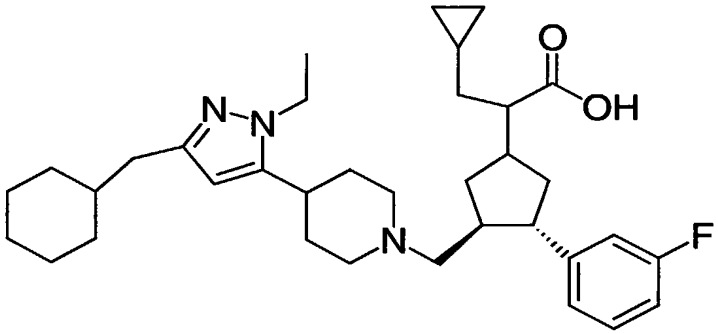

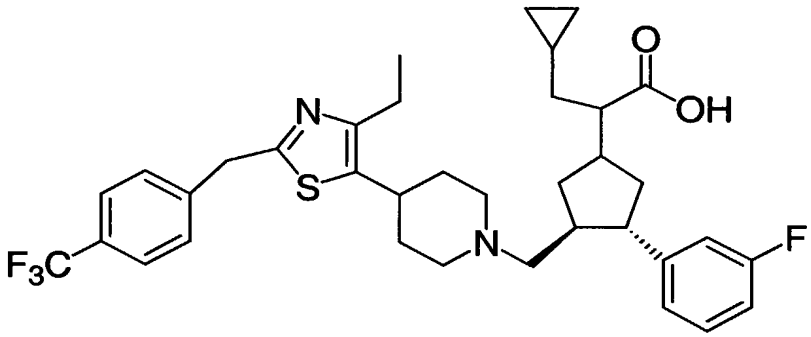

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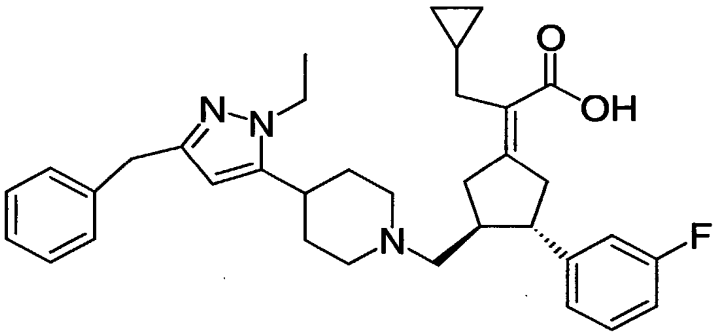
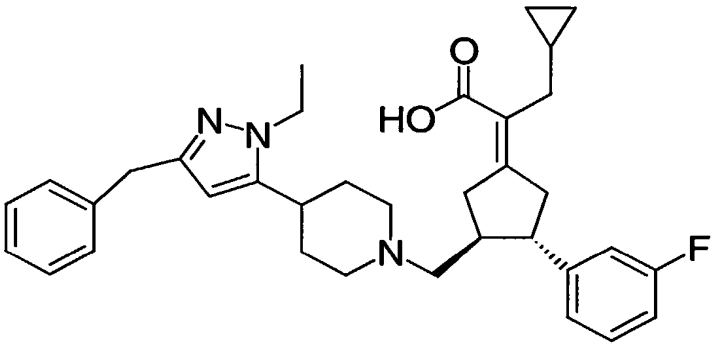
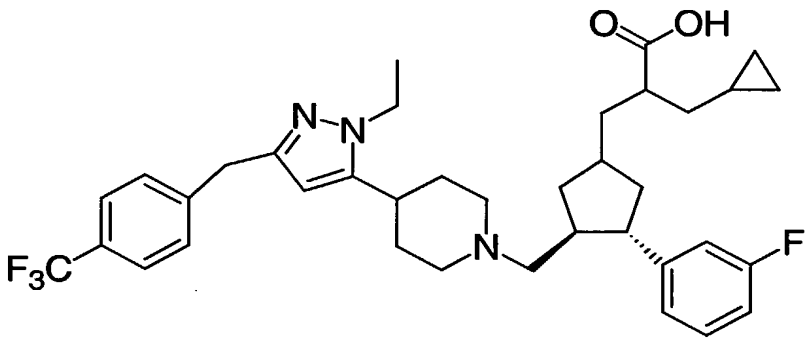
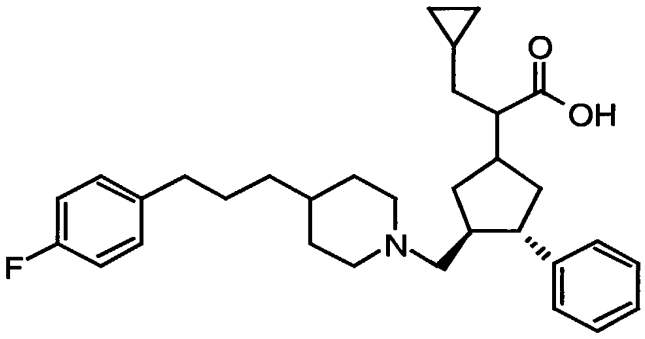


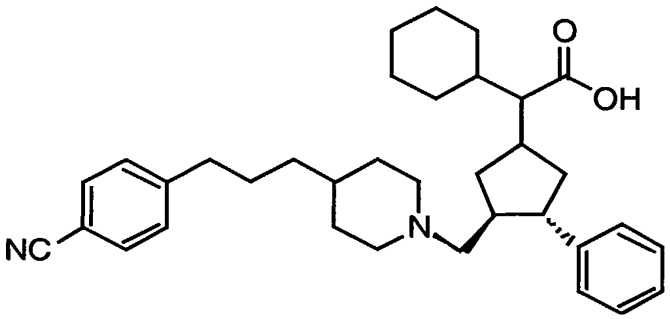


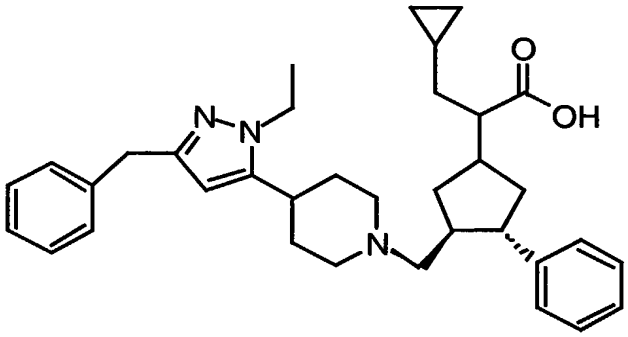


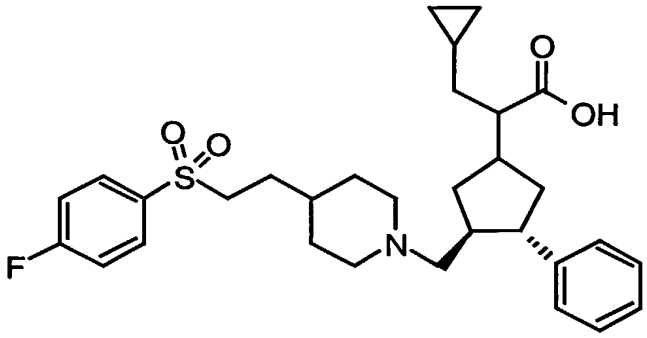
and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

An aspect of the present invention is a compound selected from the group consisting of:









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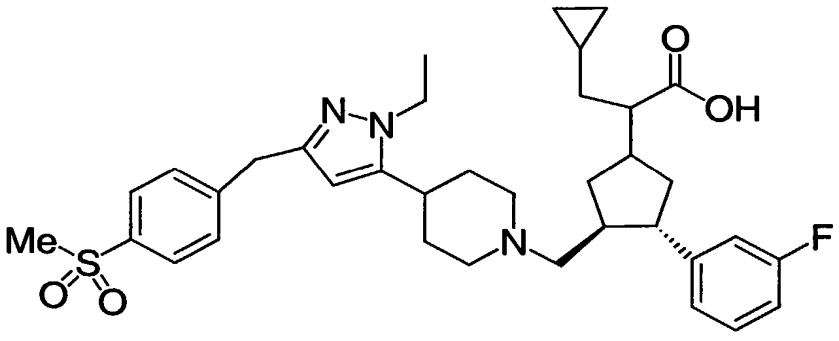

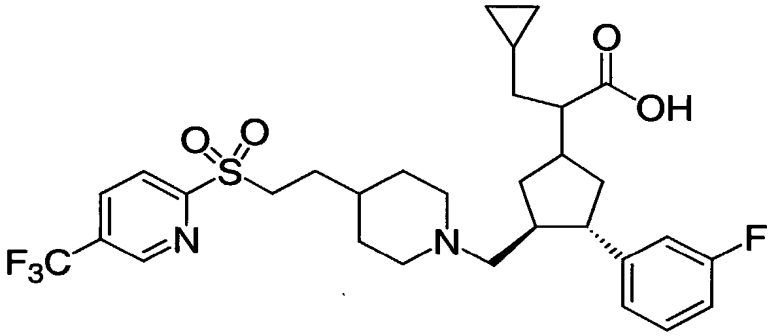

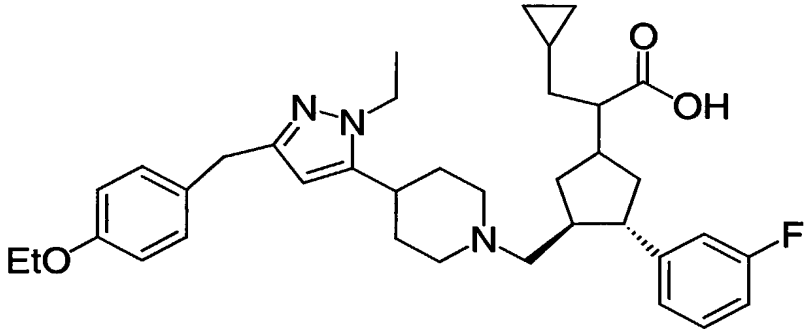

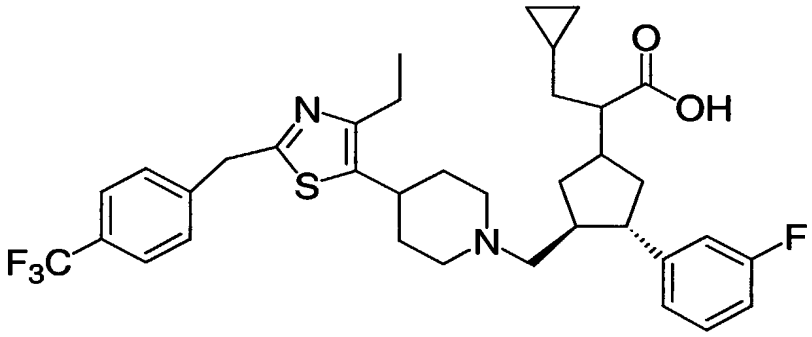

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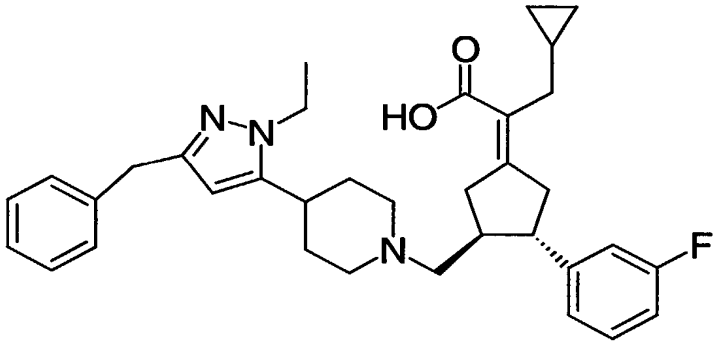
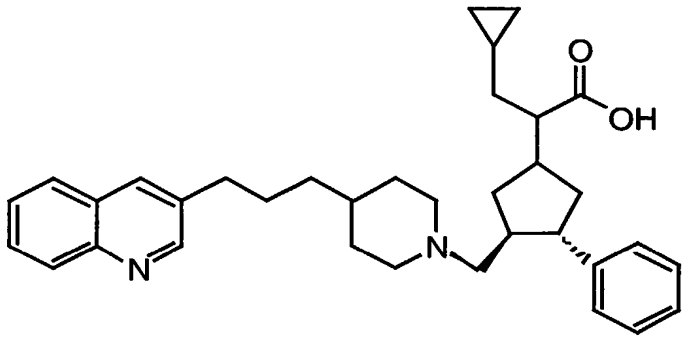




and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

The subject compounds are useful in a method of modulating chemokine receptor activity in a patient in need of such modulation comprising the administration of an effective amount of the compound.

The present invention is directed to the use of the foregoing compounds as modulators of chemokine receptor activity. In particular, these compounds are useful as modulators of the chemokine receptors, including CCR-5 and/or CCR-3.

The utility of the compounds in accordance with the present invention as modulators of chemokine receptor activity may be demonstrated by methodology known in the art, such as the assay for chemokine binding as disclosed by Van Riper, et al., J. Exp. Med., 177, 851-856 (1993) which may be readily adapted for measurement of CCR-5 binding, and the assay for CCR-3 binding as disclosed by Daugherty, et al., J. Exp. Med., 183, 2349-2354 (1996). Cell lines for expressing the receptor of interest include those naturally expressing the receptor, such as EOL-3 or THP-1, or a cell engineered to express a recombinant receptor, such as CHO, RBL-2H3, HEK-293. For example, a CCR3 transfected AML14.3D10 cell line has been placed on restricted deposit with American Type Culture Collection in Rockville, Maryland as ATCC No. CRL-12079, on April 5, 1996. The utility of the compounds in accordance with the present invention as inhibitors of the spread of HIV infection in cells may be demonstrated by methodology known in the art, such as the HIV quantitation assay disclosed by Nunberg, et al., J. Virology, 65 (9), 4887-4892 (1991).

In particular, the compounds of the following examples had activity in binding to the CCR-5 or the CCR-3 receptor in the aforementioned assays, generally with an IC_{50} of less than about 1 μM. Such a result is indicative of the intrinsic activity of the compounds in use as modulators of chemokine receptor activity.

Mammalian chemokine receptors provide a target for interfering with or promoting eosinophil and/or lymphocyte function in a mammal, such as a human. Compounds which inhibit or promote chemokine receptor function, are particularly useful for modulating eosinophil and/or lymphocyte function for therapeutic purposes. Accordingly, the present invention is directed to compounds which are useful in the prevention and/or treatment of a wide variety of inflammatory and immunoregulatory disorders and diseases, allergic diseases, atopic conditions including allergic rhinitis, dermatitis, conjunctivitis, and asthma, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis.

For example, an instant compound which inhibits one or more functions of a mammalian chemokine receptor (e.g., a human chemokine receptor) may be administered to inhibit (i.e., reduce or prevent) inflammation. As a result, one or more inflammatory processes, such as leukocyte emigration, chemotaxis, exocytosis (e.g., of enzymes, histamine) or inflammatory mediator release, is inhibited. For example, eosinophilic infiltration to inflammatory sites (e.g., in asthma) can be inhibited according to the present method.

Similarly, an instant compound which promotes one or more functions of a mammalian chemokine receptor (e.g., a human chemokine) is administered to stimulate (induce or enhance) an inflammatory response, such as leukocyte emigration, chemotaxis, exocytosis (e.g., of enzymes, histamine) or inflammatory mediator release, resulting in the beneficial stimulation of inflammatory processes. For example, eosinophils can be recruited to combat parasitic infections.

In addition to primates, such as humans, a variety of other mammals can be treated according to the method of the present invention. For instance, mammals including, but not limited to, cows, sheep, goats, horses, dogs, cats, guinea pigs, rats or other bovine, ovine, equine, canine, feline, rodent or murine species can be treated. However, the method can also be practiced in other species, such as avian species (e.g., chickens).

Diseases and conditions associated with inflammation and infection can be treated using the method of the present invention. In a preferred embodiment, the disease or condition is one in which the actions of eosinophils and/or lymphocytes are to be inhibited or promoted, in order to modulate the inflammatory response.

Diseases or conditions of humans or other species which can be treated with inhibitors of chemokine receptor function, include, but are not limited to: inflammatory or allergic diseases and conditions, including respiratory allergic

diseases such as asthma, particularly bronchial asthma, allergic rhinitis, hypersensitivity lung diseases, hypersensitivity pneumonitis, eosinophilic pneumonias (e.g., Loeffler's syndrome, chronic eosinophilic pneumonia), delayed-type hypersentitivity, interstitial lung diseases (ILD) (e.g., idiopathic pulmonary fibrosis, or ILD associated with rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, systemic sclerosis, Sjogren's syndrome, polymyositis or dermatomyositis); systemic anaphylaxis or hypersensitivity responses, drug allergies (e.g., to penicillin, cephalosporins), insect sting allergies; autoimmune diseases, such as rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, systemic lupus erythematosus, myasthenia gravis, juvenile onset diabetes; glomerulonephritis, autoimmune thyroiditis, Behcet's disease; graft rejection (e.g., in transplantation), including allograft rejection or graft-versus-host disease; inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis; spondyloarthropathies; scleroderma; psoriasis (including T-cell mediated psoriasis) and inflammatory dermatoses such an dermatitis, eczema, atopic dermatitis, allergic contact dermatitis, urticaria; vasculitis (e.g., necrotizing, cutaneous, and hypersensitivity vasculitis); eosinphilic myositis, eosinophilic fasciitis; cancers with leukocyte infiltration of the skin or organs. Other diseases or conditions in which undesirable inflammatory responses are to be inhibited can be treated, including, but not limited to, reperfusion injury, atherosclerosis, certain hematologic malignancies, cytokine-induced toxicity (e.g., septic shock, endotoxic shock), polymyositis, dermatomyositis.

Diseases or conditions of humans or other species which can be treated with promoters of chemokine receptor function, include, but are not limited to: immunosuppression, such as that in individuals with immunodeficiency syndromes such as AIDS, individuals undergoing radiation therapy, chemotherapy, therapy for autoimmune disease or other drug therapy (e.g., corticosteroid therapy), which causes immunosuppression; immunosuppression due congenital deficiency in receptor function or other causes; and infectious diseases, such as parasitic diseases, including, but not limited to helminth infections, such as nematodes (round worms); (Trichuriasis, Enterobiasis, Ascariasis, Hookworm, Strongyloidiasis, Trichinosis, filariasis); trematodes (flukes) (Schistosomiasis, Clonorchiasis), cestodes (tape worms) (Echinococcosis, Taeniasis saginata, Cysticercosis); visceral worms, visceral larva migrans (e.g., Toxocara), eosinophilic gastroenteritis (e.g., Anisaki spp., *Phocanema ssp.),* cutaneous larva migrans (*Ancylostona braziliense, Ancylostoma caninum*).

The compounds of the present invention are accordingly useful in the prevention and treatment of a wide variety of inflammatory and immunoregulatory disorders and diseases, allergic conditions, atopic conditions, as well as autoimmune pathologies.

In another aspect, the instant invention may be used to evaluate putative specific agonists or antagonists of chemokine receptors, including CCR-5 and/or CCR-3. Accordingly, the present invention is directed to the use of these compounds in the preparation and execution of screening assays for compounds which modulate the activity of chemokine receptors. For example, the compounds of this invention are useful for isolating receptor mutants, which are excellent screening tools for more potent compounds. Furthermore, the compounds of this invention are useful in establishing or determining the binding site of other compounds to chemokine receptors, e.g., by competitive inhibition. The compounds of the instant invention are also useful for the evaluation of putative specific modulators of the chemokine receptors, including CCR-5 and/or CCR-3. As appreciated in the art, thorough evaluation of specific agonists and antagonists of the above chemokine receptors has been hampered by the lack of availability of non-peptidyl (metabolically resistant) compounds with high binding affinity for these receptors. Thus the compounds of this invention are commercial products to be sold for these purposes.

The present invention is further directed to a method for the manufacture of a medicament for modulating chemokine receptor activity in humans and animals comprising combining a compound of the present invention with a pharmaceutical carrier or diluent.

The present invention is further directed to the use of these compounds in the prevention or treatment of infection by a retrovirus, in particular, the human immunodeficiency virus (HIV) and the treatment of, and delaying of the onset of consequent pathological conditions such as AIDS. Treating AIDS or preventing or treating infection by HIV is defined as including, but not limited to, treating a wide range of states of HIV infection: AIDS, ARC (AIDS related complex), both symptomatic and asymptomatic, and actual or potential exposure to HIV. For example, the compounds of this invention are useful in treating infection by HIV after suspected past exposure to HIV by, e.g., blood transfusion, organ transplant, exchange of body fluids, bites, accidental needle stick, or exposure to patient blood during surgery.

In a preferred aspect of the present invention, a subject compound may be used in a method of inhibiting the binding of a chemokine to a chemokine receptor, such as CCR-5 or CCR-3, of a target cell, which comprises contacting the target cell with an amount of the compound which is effective at inhibiting the binding of the chemokine to the chemokine receptor.

The subject treated in the methods above is a mammal, preferably a human being, male or female, in whom modulation of chemokine receptor activity is desired. "Modulation" as used herein is intended to encompass antagonism, agonism, partial antagonism, inverse agonism and/or partial agonism. In a preferred aspect of the present invention, modulation refers to antagonism of chemokine receptor activity. The term "therapeutically effective amount" means the amount of the subject compound that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician.

The term "composition" as used herein is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The terms "administration of" and or "administering a" compound should be understood to mean providing a compound of the invention to the individual in need of treatment.

Combined therapy to modulate chemokine receptor activity and thereby prevent and treat inflammatory and immunoregulatory disorders and diseases, including asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis, and those pathologies noted above is illustrated by the combination of the compounds of this invention and other compounds which are known for such utilities.

For example, in the treatment or prevention of inflammation, the present compounds may be used in conjunction with an antiinflammatory or analgesic agent such as an opiate agonist, a lipoxygenase inhibitor, such as an inhibitor of 5-lipoxygenase, a cyclooxygenase inhibitor, such as a cyclooxygenase-2 inhibitor, an interleukin inhibitor, such as an interleukin-1 inhibitor, an NMDA antagonist, an inhibitor of nitric oxide or an inhibitor of the synthesis of nitric oxide, a non-steroidal

antiinflammatory agent, or a cytokine-suppressing antiinflammatory agent, for example with a compound such as acetaminophen, asprin, codiene, fentanyl, ibuprofen, indomethacin, ketorolac, morphine, naproxen, phenacetin, piroxicam, a steroidal analgesic, sufentanyl, sunlindac, tenidap, and the like. Similarly, the instant compounds may be administered with a pain reliever; a potentiator such as caffeine, an H2-antagonist, simethicone, aluminum or magnesium hydroxide; a decongestant such as phenylephrine, phenylpropanolamine, pseudophedrine, oxymetazoline, ephinephrine, naphazoline, xylometazoline, propylhexedrine, or levo-desoxy-ephedrine; an antiitussive such as codeine, hydrocodone, caramiphen, carbetapentane, or dextramethorphan; a diuretic; and a sedating or non-sedating antihistamine. Likewise, compounds of the present invention may be used in combination with other drugs that are used in the treatment/prevention/suppression or amelioration of the diseases or conditions for which compounds of the pressent invention are useful. Such other drugs may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of the present invention. When a compound of the present invention is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound of the present invention is preferred. Accordingly, the pharmaceutical compositions of the present invention include those that also contain one or more other active ingredients, in addition to a compound of the present invention. Examples of other active ingredients that may be combined with a compound of the present invention, either administered separately or in the same pharmaceutical compositions, include, but are not limited to: (a) VLA-4 antagonists such as those described in US 5,510,332, WO95/15973, WO96/01644, WO96/06108, WO96/20216, WO96/22966, WO96/31206, WO96/40781, WO97/03094, WO97/02289, WO 98/42656, WO98/53814, WO98/53817, WO98/53818, WO98/54207, and WO98/58902; (b) steroids such as beclomethasone, methylprednisolone, betamethasone, prednisone, dexamethasone, and hydrocortisone; (c) immunosuppressants such as cyclosporin, tacrolimus, rapamycin and other FK-506 type immunosuppressants; (d) antihistamines (H1-histamine antagonists) such as bromopheniramine, chlorpheniramine, dexchlorpheniramine, triprolidine, clemastine, diphenhydramine, diphenylpyraline, tripelennamine, hydroxyzine, methdilazine, promethazine, trimeprazine, azatadine, cyproheptadine, antazoline, pheniramine pyrilamine, astemizole, terfenadine, loratadine, cetirizine, fexofenadine, descarboethoxyloratadine, and the like; (e) non-steroidal anti-asthmatics such as β2-

agonists (terbutaline, metaproterenol, fenoterol, isoetharine, albuterol, bitolterol, and pirbuterol), theophylline, cromolyn sodium, atropine, ipratropium bromide, leukotriene antagonists (zafirlukast, montelukast, pranlukast, iralukast, pobilukast, SKB-106,203), leukotriene biosynthesis inhibitors (zileuton, BAY-1005); (f) non-steroidal antiinflammatory agents (NSAIDs) such as propionic acid derivatives (alminoprofen, benoxaprofen, bucloxic acid, carprofen, fenbufen, fenoprofen, fluprofen, flurbiprofen, ibuprofen, indoprofen, ketoprofen, miroprofen, naproxen, oxaprozin, pirprofen, pranoprofen, suprofen, tiaprofenic acid, and tioxaprofen), acetic acid derivatives (indomethacin, acemetacin, alclofenac, clidanac, diclofenac, fenclofenac, fenclozic acid, fentiazac, furofenac, ibufenac, isoxepac, oxpinac, sulindac, tiopinac, tolmetin, zidometacin, and zomepirac), fenamic acid derivatives (flufenamic acid, meclofenamic acid, mefenamic acid, niflumic acid and tolfenamic acid), biphenylcarboxylic acid derivatives (diflunisal and flufenisal), oxicams (isoxicam, piroxicam, sudoxicam and tenoxican), salicylates (acetyl salicylic acid, sulfasalazine) and the pyrazolones (apazone, bezpiperylon, feprazone, mofebutazone, oxyphenbutazone, phenylbutazone); (g) cyclooxygenase-2 (COX-2) inhibitors; (h) inhibitors of phosphodiesterase type IV (PDE-IV); (i) other antagonists of the chemokine receptors, especially CXCR-4, CCR-1, CCR-2, CCR-3 and CCR-5; (j) cholesterol lowering agents such as HMG-CoA reductase inhibitors (lovastatin, simvastatin and pravastatin, fluvastatin, atorvastatin, and other statins), sequestrants (cholestyramine and colestipol), nicotinic acid, fenofibric acid derivatives (gemfibrozil, clofibrat, fenofibrate and benzafibrate), and probucol; (k) anti-diabetic agents such as insulin, sulfonylureas, biguanides (metformin), α-glucosidase inhibitors (acarbose) and glitazones (troglitazone and pioglitazone); (l) preparations of interferon beta (interferon beta-1α, interferon beta-1β); (m) other compounds such as 5-aminosalicylic acid and prodrugs thereof, antimetabolites such as azathioprine and 6-mercaptopurine, and cytotoxic cancer chemotherapeutic agents. The weight ratio of the compound of the compound of the present invention to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the present invention is combined with an NSAID the weight ratio of the compound of the present invention to the NSAID will generally range from about 1000:1 to about 1:1000, preferably about 200:1 to about 1:200. Combinations of a compound of the present invention and other active ingredients will generally also be

within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

The present invention is further directed to combinations of the present compounds with one or more agents useful in the prevention or treatment of AIDS. For example, the compounds of this invention may be effectively administered, whether at periods of pre-exposure and/or post-exposure, in combination with effective amounts of the AIDS antivirals, immunomodulators, anti-infectives, or vaccines known to those of ordinary skill in the art.

ANTIVIRALS

Drug Name	Manufacturer	Indication
097	Hoechst/Bayer	HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase inhibitor)
141 W94	Glaxo Wellcome	HIV infection, AIDS, ARC (protease inhibitor)
1592U89	Glaxo Wellcome	HIV infection, AIDS, ARC
Acemannan	Carrington Labs (Irving, TX)	ARC
Acyclovir	Burroughs Wellcome	HIV infection, AIDS, ARC, in combination with AZT
AD-439	Tanox Biosystems	HIV infection, AIDS, ARC
AD-519	Tanox Biosystems	HIV infection, AIDS, ARC
Adefovir dipivoxil	Gilead Sciences	HIV infection

AL-721	Ethigen (Los Angeles, CA)	ARC, PGL HIV positive, AIDS
Alpha Interferon	Glaxo Wellcome	Kaposi's sarcoma, HIV in combination w/Retrovir
Ansamycin LM 427	Adria Laboratories (Dublin, OH) Erbamont (Stamford, CT)	ARC
Antibody which neutralizes pH labile alpha aberrant Interferon	Advanced Biotherapy Concepts (Rockville, MD)	AIDS, ARC
AR177	Aronex Pharm	HIV infection, AIDS, ARC
beta-fluoro-ddA	Nat'l Cancer Institute	AIDS-associated diseases
(-) 6-Chloro-4(S)-cyclopropylethynyl-4(S)-trifluoro-methyl-1,4-dihydro-2H-3,1-benzoxazin-2-one	Merck	HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase inhibitor)
CI-1012	Warner-Lambert	HIV-1 infection
Cidofovir	Gilead Science	CMV retinitis, herpes, papillomavirus
Curdlan sulfate	AJI Pharma USA	HIV infection
Cytomegalovirus immune globin	MedImmune	CMV retinitis
Cytovene Ganciclovir	Syntex	sight threatening CMV peripheral CMV retinitis
Delaviridine	Pharmacia-Upjohn	HIV infection, AIDS, ARC (protease inhibitor)

Dextran Sulfate	Ueno Fine Chem. Ind. Ltd. (Osaka, Japan)	AIDS, ARC, HIV positive asymptomatic
ddC Dideoxycytidine	Hoffman-La Roche	HIV infection, AIDS, ARC
ddI Dideoxyinosine	Bristol-Myers Squibb	HIV infection, AIDS, ARC; combination with AZT/d4T
DMP-450	AVID (Camden, NJ)	HIV infection, AIDS, ARC (protease inhibitor)
EL10	Elan Corp, PLC (Gainesville, GA)	HIV infection
Efavirenz (DMP 266) (-) 6-Chloro-4(S)-cyclopropylethynyl-4(S)-trifluoro-methyl-1,4-dihydro-2H-3,1-benzoxazin-2-one,	DuPont (SUSTIVA®), Merck (STOCRIN®)	HIV infection, AIDS, ARC (non-nucleoside RT inhibitor)
Famciclovir	Smith Kline	herpes zoster, herpes simplex
FTC	Emory University	HIV infection, AIDS, ARC (reverse transcriptase inhibitor)
GS 840	Gilead	HIV infection, AIDS, ARC (reverse transcriptase inhibitor)
GW 141	Glaxo Welcome	HIV infection, AIDS, ARC (protease inhibitor)

GW 1592	Glaxo Welcome	HIV infection, AIDS, ARC (reverse transcriptase inhibitor)
HBY097	Hoechst Marion Roussel	HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase inhibitor)
Hypericin	VIMRx Pharm.	HIV infection, AIDS, ARC
Recombinant Human Interferon Beta	Triton Biosciences (Almeda, CA)	AIDS, Kaposi's sarcoma, ARC
Interferon alfa-n3	Interferon Sciences	ARC, AIDS
Indinavir	Merck	HIV infection, AIDS, ARC, asymptomatic HIV positive, also in combination with AZT/ddI/ddC
Compound A	Merck	HIV infection, AIDS, ARC, asymptomatic HIV positive
ISIS 2922	ISIS Pharmaceuticals	CMV retinitis
KNI-272	Nat'l Cancer Institute	HIV-assoc. diseases
Lamivudine, 3TC	Glaxo Wellcome	HIV infection, AIDS, ARC (reverse transcriptase inhibitor); also with AZT
Lobucavir	Bristol-Myers Squibb	CMV infection
Nelfinavir	Agouron Pharmaceuticals	HIV infection, AIDS, ARC (protease inhibitor)

Nevirapine	Boeheringer Ingleheim	HIV infection, AIDS, ARC (protease inhibitor)
Novapren	Novaferon Labs, Inc. (Akron, OH)	HIV inhibitor
Peptide T Octapeptide Sequence	Peninsula Labs (Belmont, CA)	AIDS
Trisodium Phosphonoformate	Astra Pharm. Products, Inc	CMV retinitis, HIV infection, other CMV infections
PNU-140690	Pharmacia Upjohn	HIV infection, AIDS, ARC (protease inhibitor)
Probucol	Vyrex	HIV infection, AIDS
RBC-CD4	Sheffield Med. Tech (Houston TX)	HIV infection, AIDS, ARC
Ritonavir	Abbott	HIV infection, AIDS, ARC (protease inhibitor)
Saquinavir	Hoffmann-LaRoche	HIV infection, AIDS, ARC (protease inhibitor)
Stavudine; d4T Didehydrodeoxy-thymidine	Bristol-Myers Squibb	HIV infection, AIDS, ARC
T-20	Trimeris	HIV infection, AIDS, ARC
Valaciclovir	Glaxo Wellcome	genital HSV & CMV infections
Virazole Ribavirin	Viratek/ICN (Costa Mesa, CA)	asymptomatic HIV positive, LAS, ARC
Amprenivir VX-478	Vertex	HIV infection, AIDS, ARC

Zalcitabine	Hoffmann-La Roche	HIV infection, AIDS, ARC, with AZT
Zidovudine; AZT	Glaxo Wellcome	HIV infection, AIDS, ARC, Kaposi's sarcoma, in combination with other therapies
ABT-378	Abbott	HIV infection, AIDS, ARC (protease inhibitor)
JE2147/AG1776	Agouron	HIV infection, AIDS, ARC (protease inhibitor)
T-20 T-1249	Trimeris	HIV infection, AIDS, ARC (fusion inhibitor)
BMS 232632	Bristol-Myers-Squibb	HIV infection, AIDS, ARC (protease inhibitor)

IMMUNO-MODULATORS

Drug Name	Manufacturer	Indication
AS-101	Wyeth-Ayerst	AIDS
Bropirimine	Pharmacia Upjohn	advanced AIDS
Acemannan	Carrington Labs, Inc. (Irving, TX)	AIDS, ARC
CL246,738	American Cyanamid Lederle Labs	AIDS, Kaposi's sarcoma
EL10	Elan Corp, PLC (Gainesville, GA)	HIV infection
Gamma Interferon	Genentech	ARC, in combination w/TNF (tumor necrosis factor)
Granulocyte Macrophage Colony Stimulating Factor	Genetics Institute Sandoz	AIDS

Granulocyte Macrophage Colony Stimulating Factor	Hoeschst-Roussel Immunex	AIDS
Granulocyte Macrophage Colony Stimulating Factor	Schering-Plough	AIDS, combination w/AZT
HIV Core Particle Immunostimulant	Rorer	seropositive HIV
IL-2 Interleukin-2	Cetus	AIDS, in combination w/AZT
IL-2 Interleukin-2	Hoffman-La Roche Immunex	AIDS, ARC, HIV, in combination w/AZT
IL-2 Interleukin-2 (aldeslukin)	Chiron	AIDS, increase in CD4 cell counts
Immune Globulin Intravenous (human)	Cutter Biological (Berkeley, CA)	pediatric AIDS, in combination w/AZT
IMREG-1	Imreg (New Orleans, LA)	AIDS, Kaposi's sarcoma, ARC, PGL
IMREG-2	Imreg (New Orleans, LA)	AIDS, Kaposi's sarcoma, ARC, PGL
Imuthiol Diethyl Dithio Carbamate	Merieux Institute	AIDS, ARC
Alpha-2 Interferon	Schering Plough	Kaposi's sarcoma w/AZT, AIDS
Methionine-Enkephalin	TNI Pharmaceutical (Chicago, IL)	AIDS, ARC
MTP-PE Muramyl-Tripeptide	Ciba-Geigy Corp.	Kaposi's sarcoma
Granulocyte Colony Stimulating Factor	Amgen	AIDS, in combination w/AZT

Remune	Immune Response Corp.	immunotherapeutic
rCD4	Genentech	AIDS, ARC
Recombinant Soluble Human CD4		
rCD4-IgG hybrids		AIDS, ARC
Recombinant Soluble Human CD4	Biogen	AIDS, ARC
Interferon Alfa 2a	Hoffman-La Roche	Kaposi's sarcoma AIDS, ARC, in combination w/AZT
SK&F106528 Soluble T4	Smith Kline	HIV infection
Thymopentin	Immunobiology Research Institute	HIV infection
Tumor Necrosis Factor; TNF	Genentech	ARC, in combination w/gamma Interferon
etanercept	Immunex Corp (Enbrel®)	rheumatoid arthritis
infliximab	Centocor (Remicade®)	rheumatoid arthritis and Crohn's disease

ANTI-INFECTIVES

Drug Name	Manufacturer	Indication
Clindamycin with Primaquine	Pharmacia Upjohn	PCP
Fluconazole	Pfizer	cryptococcal meningitis, candidiasis
Pastille Nystatin Pastille	Squibb Corp.	prevention of oral candidiasis
Ornidyl Eflornithine	Merrell Dow	PCP

Pentamidine Isethionate (IM & IV)	LyphoMed (Rosemont, IL)	PCP treatment
Trimethoprim		antibacterial
Trimethoprim/sulfa		antibacterial
Piritrexim	Burroughs Wellcome	PCP treatment
Pentamidine isethionate for inhalation	Fisons Corporation	PCP prophylaxis
Spiramycin	Rhone-Poulenc	cryptosporidial diarrhea
Intraconazole-R51211	Janssen Pharm.	histoplasmosis; cryptococcal meningitis
Trimetrexate	Warner-Lambert	PCP

OTHER

Drug Name	Manufacturer	Indication
Daunorubicin	NeXstar, Sequus	Karposi's sarcoma
Recombinant Human Erythropoietin	Ortho Pharm. Corp.	severe anemia assoc. with AZT therapy
Recombinant Human Growth Hormone	Serono	AIDS-related wasting, cachexia
Leukotriene B4 Receptor Antagonist	-	HIV infection
Megestrol Acetate	Bristol-Myers Squibb	treatment of anorexia assoc. w/AIDS
Soluble CD4 Protein and Derivatives	-	HIV infection
Testosterone	Alza, Smith Kline	AIDS-related wasting
Total Enteral Nutrition	Norwich Eaton Pharmaceuticals	diarrhea and malabsorption related to AIDS

It will be understood that the scope of combinations of the compounds of this invention with AIDS antivirals, immunomodulators, anti-infectives or vaccines is not limited to the list in the above Table, but includes in principle any combination with any pharmaceutical composition useful for the treatment of AIDS.

Preferred combinations are simultaneous or alternating treatments with a compound of the present invention and an inhibitor of HIV protease and/or a non-nucleoside inhibitor of HIV reverse transcriptase. An optional fourth component in the combination is a nucleoside inhibitor of HIV reverse transcriptase, such as AZT, 3TC, ddC or ddI. Preferred agents for combination therapy include: Zidovudine, Lamivudine, Stavudine, Efavirenz, Ritonavir, Nelfinavir, Abacavir, Indinavir, 141-W94 (4-amino-N-((2 syn,3S)-2-hydroxy-4-phenyl-3-((S)-tetrahydrofuran-3-yloxycarbonylamino)-butyl)-N-isobutyl-benzenesulfonamide), N-(2(R)-hydroxy-1(S)-indanyl)-2(R)-phenylmethyl-4-(S)-hydroxy-5-(1-(4-(2-benzo[b]furanylmethyl)-2(S)-N'(t-butylcarbox-amido)-piperazinyl))-pentaneamide, and Delavirdine. A preferred inhibitor of HIV protease is indinavir, which is the sulfate salt of N-(2(R)-hydroxy-1(S)-indanyl)-2(R)-phenylmethyl-4-(S)-hydroxy-5-(1-(4-(3-pyridyl-methyl)-2(S)-N'-(t-butylcarbo-xamido)-piperazinyl))-pentane-amide ethanolate, and is synthesized according to U.S. 5,413,999. Indinavir is generally administered at a dosage of 800 mg three times a day. Other preferred inhibitors of HIV protease include nelfinavir and ritonavir. Preferred non-nucleoside inhibitors of HIV reverse transcriptase include (-) 6-chloro-4(S)-cyclopropylethynyl-4(S)-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one, which may be prepared by methods disclosed in EP 0,582,455. The preparation of ddC, ddI and AZT are also described in EPO 0,484,071. These combinations may have unexpected effects on limiting the spread and degree of infection of HIV. Preferred combinations with the compounds of the present invention include the following: (1) Zidovudine and Lamivudine; (2) Stavudine and Lamivudine; (3) Efavirenz; (4) Ritoavir; (5) Nelfinavir; (6) Abacavir; (7) Indinavir; (8) 141-W94; and (9) Delavirdine. Preferred combinations with the compounds of the present invention further include the following (1) indinavir, with efavirenz or (-) 6-chloro-4(S)-cyclopropylethynyl-4(S)-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one, and, optionally, AZT and/or 3TC and/or ddI and/or ddC; (2) indinavir, and any of AZT and/or ddI and/or ddC.

Compound A in the foregoing Table is N-(2(R)-hydroxy-1(S)-indanyl)-2(R)-phenylmethyl-4(S)-hydroxy-5-(1-(4-(2-benzo[b]furanylmethyl)-2(S)-N'-(t-

butylcarboxamido)-piperazinyl))pentaneamide, preferably administered as the sulfate salt. Compound A can be prepared as described in US 5646148.

In such combinations the compound of the present invention and other active agents may be administered separately or in conjunction. In addition, the administration of one element may be prior to, concurrent to, or subsequent to the administration of other agent(s).

The compounds of the present invention may be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous, ICV, intracisternal injection or infusion, subcutaneous injection, or implant), by inhalation spray, nasal, vaginal, rectal, sublingual, or topical routes of administration and may be formulated, alone or together, in suitable dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles appropriate for each route of administration. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle, sheep, dogs, cats, monkeys, etc., the compounds of the invention are effective for use in humans.

The pharmaceutical compositions for the administration of the compounds of this invention may conveniently be presented in dosage unit form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general, the pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition the active object compound is included in an amount sufficient to produce the desired effect upon the process or condition of diseases. As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting

of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the techniques described in the U.S. Patents 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxy- propylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally- occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose

any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of the present invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compounds of the present invention are employed. (For purposes of this application, topical application shall include mouthwashes and gargles.)

The pharmaceutical composition and method of the present invention may further comprise other therapeutically active compounds as noted herein which are usually applied in the treatment of the above mentioned pathological conditions.

In the treatment or prevention of conditions which require chemokine receptor modulation an appropriate dosage level will generally be about 0.01 to 500 mg per kg patient body weight per day which can be administered in single or multiple doses. Preferably, the dosage level will be about 0.1 to about 250 mg/kg per day; more preferably about 0.5 to about 100 mg/kg per day. A suitable dosage level may be about 0.01 to 250 mg/kg per day, about 0.05 to 100 mg/kg per day, or about 0.1 to 50 mg/kg per day. Within this range the dosage may be 0.05 to 0.5, 0.5 to 5 or 5 to 50 mg/kg per day. For oral administration, the compositions are preferably provided in the form of tablets containing 1.0 to 1000 milligrams of the active ingredient, particularly 1.0, 5.0, 10.0, 15.0. 20.0, 25.0, 50.0, 75.0, 100.0, 150.0, 200.0, 250.0, 300.0, 400.0, 500.0, 600.0, 750.0, 800.0, 900.0, and 1000.0 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

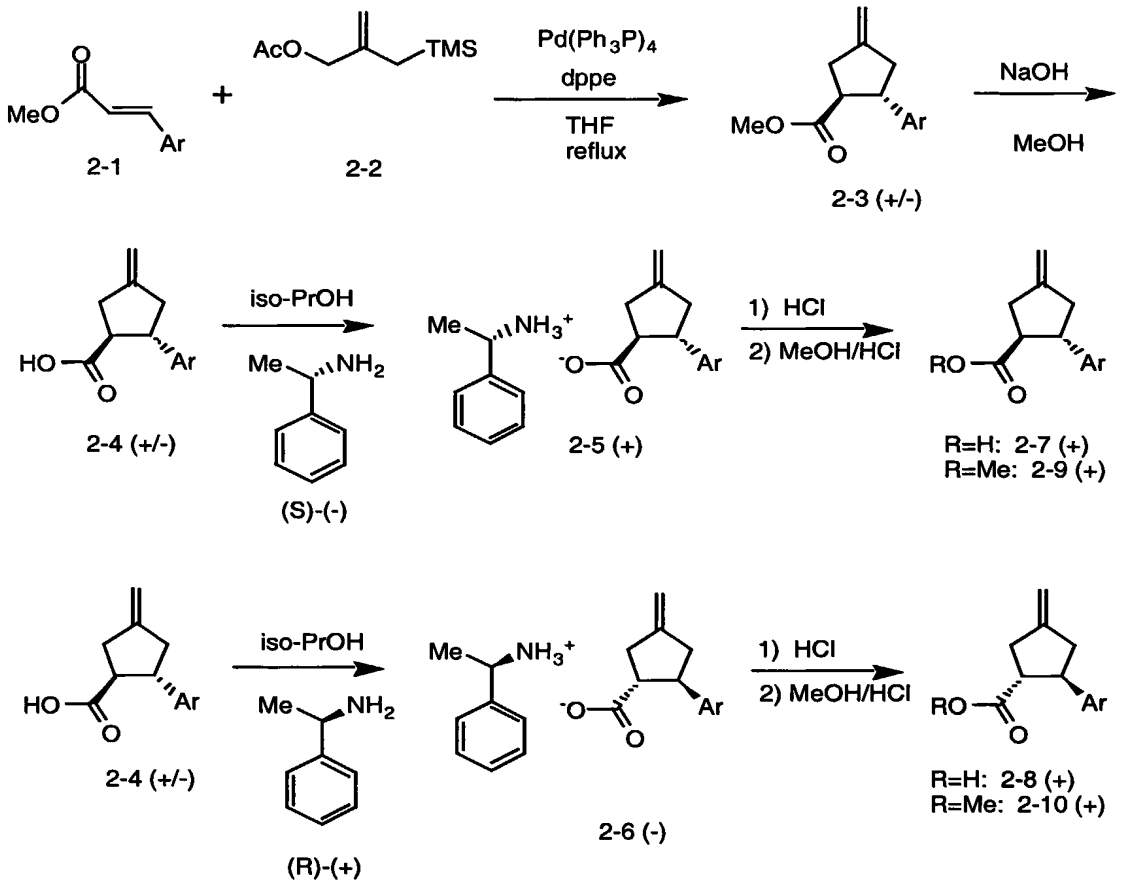
Several methods for preparing the compounds of this invention are illustrated in the following Schemes and Examples. Starting materials are commercially available, are made by known procedures or are prepared as illustrated.

SCHEME 1

1-1 1-2 1-3

The preparation of cinnamate esters such as 1-3 as intermediates that can be used for the synthesis of compounds within the scope of the instant invention is detailed in Scheme 1. Cinnamate esters of structure 1-3 can be obtained commercially or can be synthesized by reacting a suitable aromatic aldehyde 1-1 with a phosphonoacetate such as 1-2 in the presence of sodium hydride or other bases such as sodium, lithium or potassium hexamethyldisilazide, potassium t-butoxide, and the like. The aldehyde 1-1 can be obtained commercially or can be prepared in a variety of ways from commercial materials (see March J. "Advanced Organic Chemistry", 4th ed., John Wiley & Sons, New York, pp. 1270-1271 (1992)).

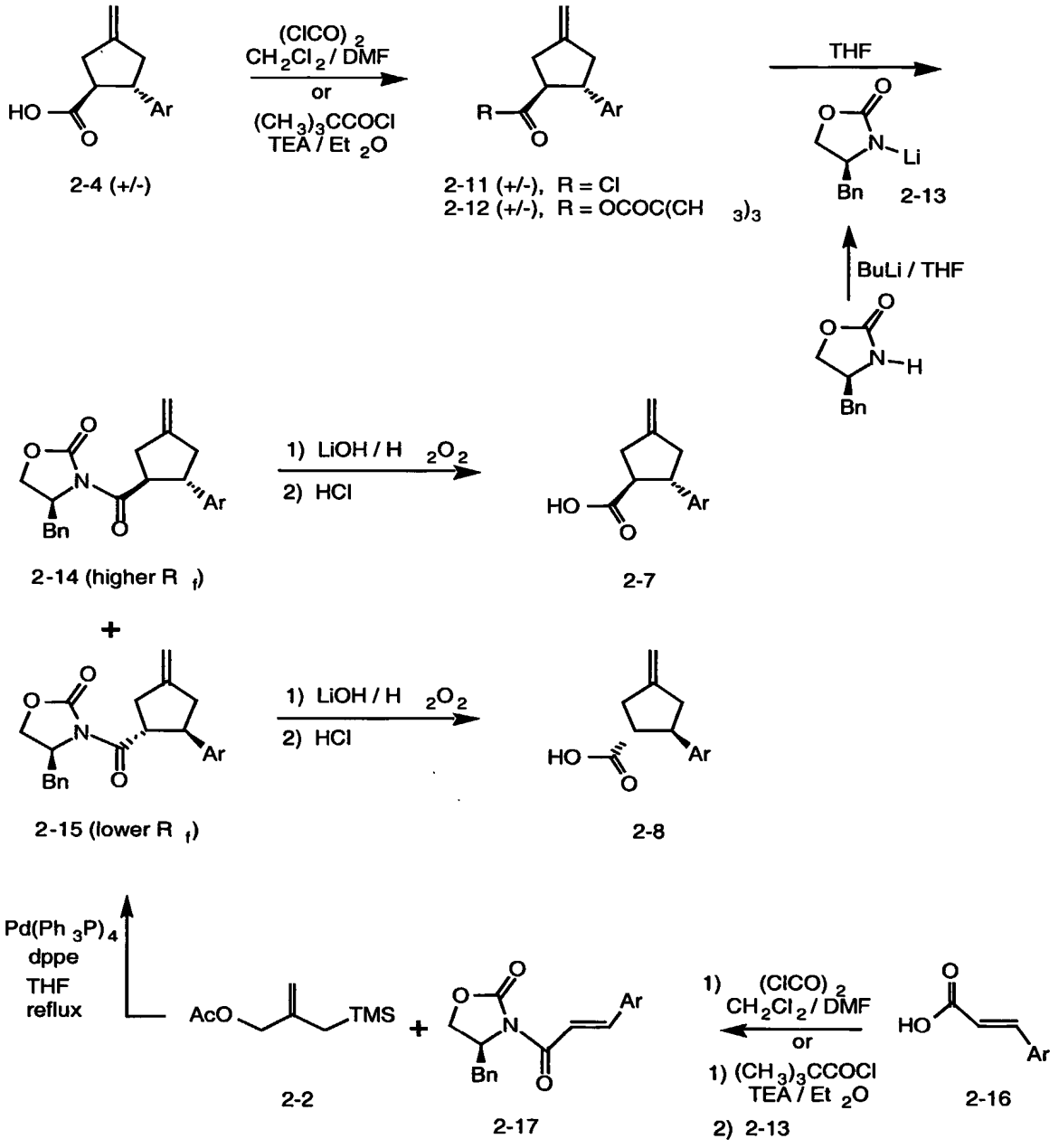
SCHEME 2



A preparation of cyclopentane intermediates having a C-4 aryl substituent within the scope of the instant invention is detailed in Scheme 2 and can be used to prepare non-racemic cyclopentane derivatives when the resolution steps are done. Treatment of a *trans*-cinnamic ester such as 2-1 (see Scheme 1) with 2-((trimethylsilyl)methyl)-2-propen-1-yl acetate (2-2) in the presence of a catalytic amount of tetrakis(triphenylphosphine) palladium (0) and 1,2-bis(diphenylphosphino)ethane in THF at reflux afforded the exo-methylene cyclopentane 2-3. Hydrolysis of the ester can be done several ways, such as with aqueous sodium or lithium hydroxide in methanol or THF, to obtain the racemic acid 2-4. Resolution of the enantiomers can be accomplished by fractional crystallization from isopropanol, or other suitable solvents, of the salts with either (R)-(+)- or (S)-(-)-α-methylbenzyl amine to give the salts 2-5 and 2-6. The non-racemic acids 2-7 and 2-8 are recovered by acidification and extraction. Reesterification to 2-9 and 2-10 can

be done in a variety of ways, such as with trimethylsilyldiazomethane or acid catalyzed esterification in methanol.

SCHEME 2A



2-4 (+/-)

2-11 (+/-), R = Cl
2-12 (+/-), R = OCOC(CH 3)3

2-13

2-14 (higher R f)

2-7

2-15 (lower R f)

2-8

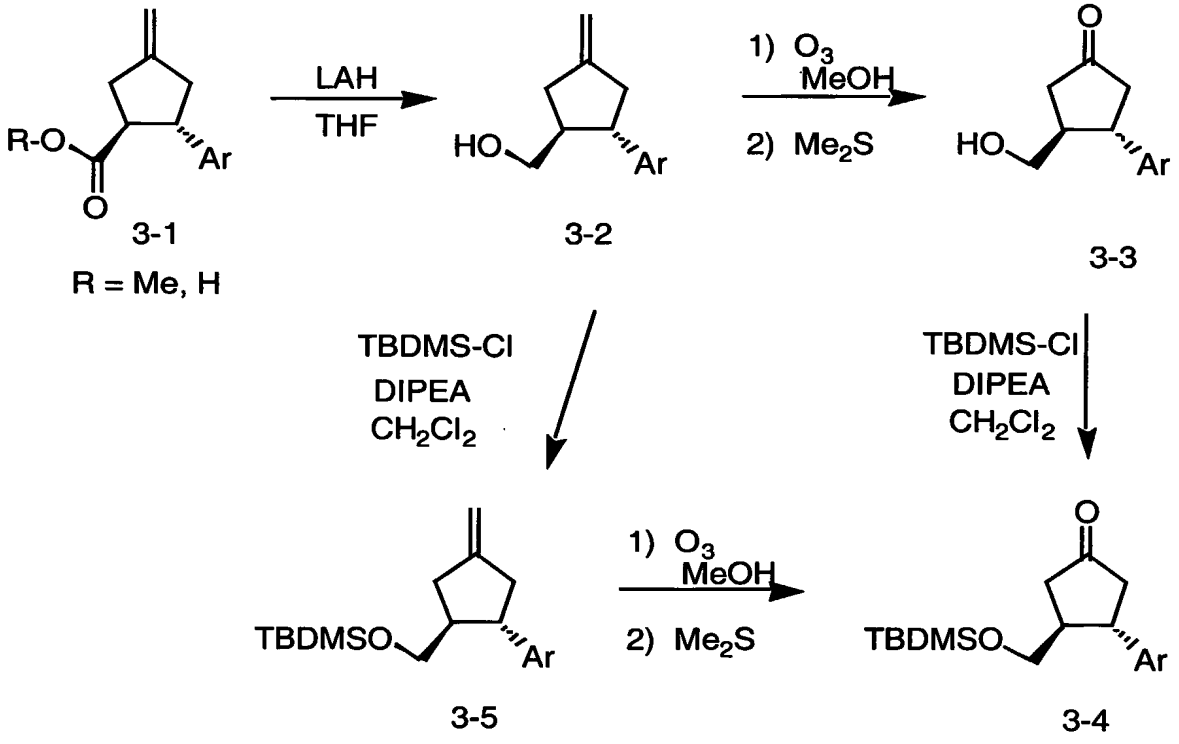
2-2

2-17

2-16

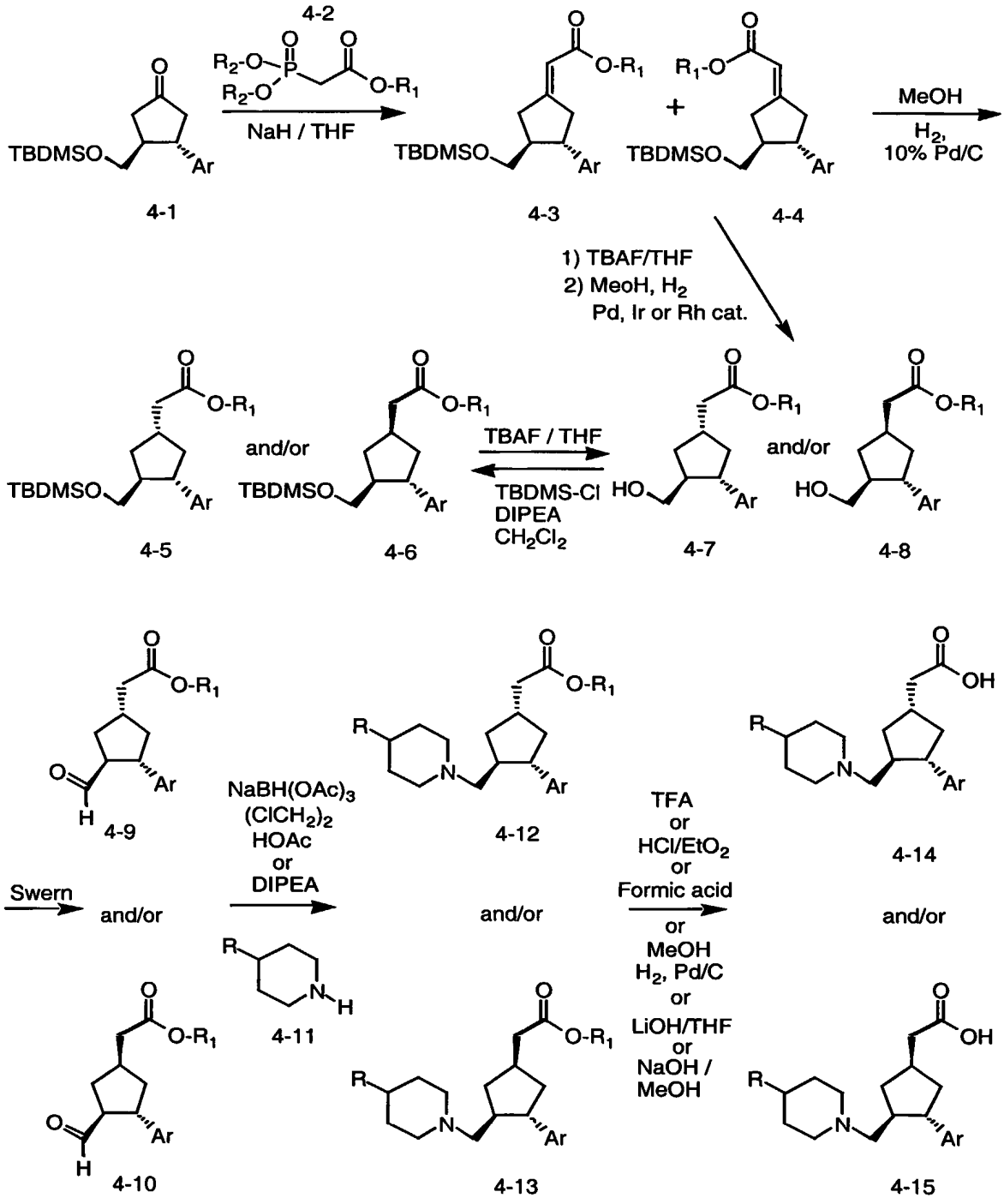
An alternative preparation of non-racemic cyclopentane intermediates having a C-4 aryl substituent within the scope of the instant invention is detailed in Scheme 2A. Conversion of the cyclopentane acid 2-4 to the acid chloride 2-11 under standard conditions, such as with oxalyl chloride in methylene chloride with a catalytic amount of DMF, or to the mixed anhydride 2-12, prepared *in situ* with trimethylacetyl chloride in ether with TEA as base, followed by reaction with the performed lithium salt of (S)-(-)-4-benzyl-2-oxazolidinone 2-13, afforded the two non-racemic diastereomeric products 2-14 and 2-15, which are then separable by chromatography. Hydrolysis of each diastereomer under standard conditions, such as with lithium hydroxide and hydrogen peroxide, affords the two non-racemic acids 2-7 and 2-8. Alternatively, in order to obtain an enhanced amount of the desired diastereomer 2-14 before separation, similar conversion of the starting *trans* -cinnamic acid 2-16 (Scheme 1) to the chiral *trans* -cinnamate 2-17 followed by the ring formation reaction with 2-((trimethylsilyl)methyl)-2-propen-1-yl acetate (2-2) as detailed in Scheme 2A affords a 60 : 40 product mixture of 2-14 : 2-15.

SCHEME 3



The preparation of further cyclopentane intermediates having a C-4 aryl substituent within the scope of the instant invention is detailed in Scheme 3 and can be used to prepare racemic and non-racemic cyclopentane derivatives. Reduction of ester 3-1 (R = Me) (either racemic or non-racemic) (from Scheme 2), for example, with lithium borohydride, diisobutylaluminum hydride, lithium aluminum hydride, or sodium bis(2-methoxyethoxy)aluminum hydride in a suitable solvent, such as ether or THF, provides the primary alcohol 3-2. Alternatively, reduction of the acid 3-1 (R = H) (either racemic or non-racemic) (from Scheme 2 or 2B), for example with lithium aluminum hydride in THF, will also afford the alcohol 3-2. In cases where the Ar moiety is not amenable to salt resolution as detailed in Scheme 2, an alternative resolution can often be achieved using chiral HPLC methods to separate the enantiomers of 3-2. Ozonolysis of the exo-methylene can be done by treating a solution of 3-2 in a suitable solvent, such as methanol or methylene chloride, at reduced temperature, preferably at -70 °C, followed by a reductive work-up with excess dimethyl sulfide at -70 °C to room temperature to afford the ketone 3-3. If required for further functionalization of the ketone, the alcohol can be protected with a t-butyldimethylsilyl group by reaction of 3-3 in a suitable solvent, such as methylene chloride or THF, with t-butyldimethylsilyl chloride in the presence of a hindered base, such as TEA or DIPEA. Alternatively, the exo-methylene-alcohol 3-2 can be protected with the t-butyldimethylsilyl group as above to give 3-5 prior to the ozonolysis to afford the same alcohol protected intermediate 3-4.

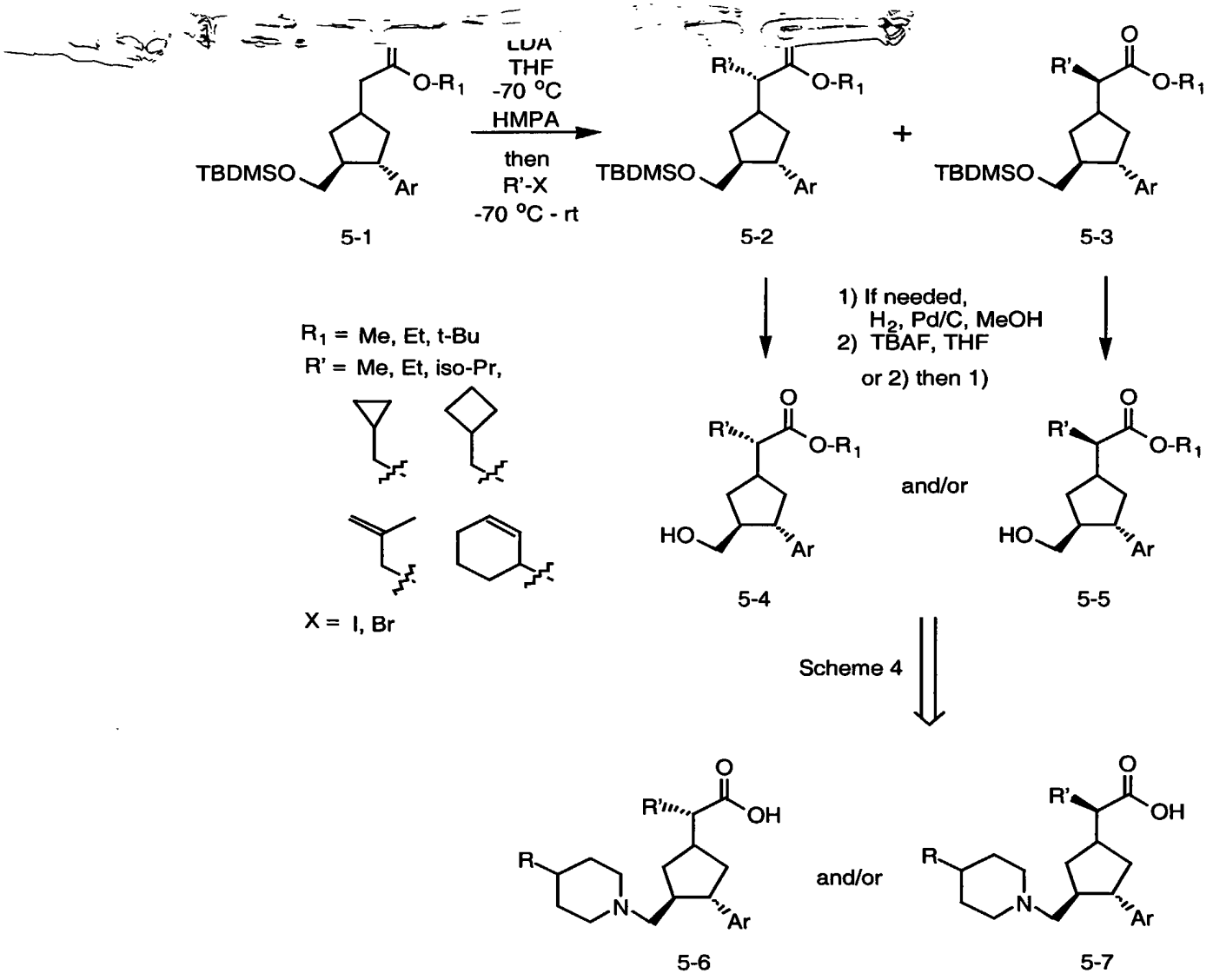
SCHEME 4


4-2
NaH / THF
MeOH
H2,
10% Pd/C
4-1
4-3
4-4
1) TBAF/THF
2) MeoH, H2
Pd, Ir or Rh cat.
and/or
TBAF / THF
TBDMS-Cl
DIPEA
CH2Cl2
4-5
4-6
4-7
4-8
4-9
NaBH(OAc)3
(ClCH2)2
HOAc
or
DIPEA
TFA
or
HCl/EtO2
or
Formic acid
or
MeOH
H2, Pd/C
or
LiOH/THF
or
NaOH /
MeOH
Swern
4-10
4-11
4-12
4-13
4-14
4-15

A route for the preparation of some 1,3,4-trisubstituted cyclopentanes within the scope of the instant invention is given in Scheme 4. Reaction of ketone 4-1 (from Scheme 3) with a dialkylphosphonoacetic acid ester such as 4-2 (R_1 = Et, t-Bu, Bn, PMB; R_2 = Me, Et) (Horner-Wadsworth-Emmons modified ylid reaction) in a suitable solvent, such as THF, dimethylsulfoxide or DMF, in the presence of a strong base, such as sodium hydride or lithium hexamethyldisilazide, at 0 to 70 °C, preferably at rt, affords a mixture of double bond products 4-3 and 4-4. Removal of the TBDMS (see below) group allows for the chromatographic separation of these isomers if desired. Normally, these were hydrogenated under standard conditions, such as in methanol at atmospheric to 60 psi of hydrogen in the presence of a palladium catalyst, such as 10% palladium on carbon or 20% palladium hydroxide on carbon (Pearlman's catalyst) to the cyclopentane acetic acid derivatives as a mixture of the C-1 isomers 4-5 and 4-6, with 4-6 usually being the predominant isomeric product, the ratio depending on conditions and the catalyst used. Since the TBDMS group is prone to cleavage under these conditions to give 4-7 and 4-8, the hydroxy group can be reprotected using standard conditions with TBDMS-Cl (see Scheme 3). Alternatively, the TBDMS group can be completely removed using either acidic alcohol, such as HCl in methanol, or using TBAF in THF, both at 0 °C to rt to afford 4-7 and 4-8, which can be separated by chromatography. Alternatively, the TBDMS group can be removed prior to the hydrogenation under acidic conditions or with TBAF (see above). Hydrogenation of the intermediate alcohol under standard conditions as above or with a hydroxy directed catalyst, such as (bicyclo[2.2.1]hepta-2,5-diene)[1,4-bis(diphenylphosphino)butane]rhodium(I) tetrafluoroborate or (1,5-cyclooctadiene)(pyridine)(tricyclohexylphosphine)iridium (I) hexafluorophosphate, in methylene chloride or THF, can afford predominantly the other isomeric product 4-7. Oxidation of 4-7 and/or 4-8 to the aldehyde(s) 4-9 and/or 4-10 can be carried out under numerous conditions, such as with DMSO and oxalyl chloride at low temperature, followed by triethylamine (Swern oxidation), with the Dess-Martin periodinane, with *N*-methylmorpholine in the presence of a catalytic amount of TPAP, or with various chromium trioxide-based reagents (see March J. "Advanced Organic Chemistry", 4th ed., John Wiley & Sons, New York, pp. 1167-1171 (1992)). Reductive alkylation of a cyclic amine, such as piperidine 4-11 (see Schemes 12 to 29), using for example sodium triacetoxyborohydride or sodium cyanoborohydride in a suitable solvent such as methylene chloride, 1,2-dichloroethane, THF, acetonitrile or methanol, with 4-9 and/or 4-10 then provides a 3-((4-(substituted)piperidin-1-

yl)methyl)cyclopentane derivative 4-12 and/or 4-13 which also may be separable by chromatography. When R_1 is t-Bu or PMB, final deprotection of the acetic acid ester to give 4-14 and/or 4-15 can be done using acidic conditions, such as HCl in ether, formic acid or TFA. When R_1 is an alkyl ester, standard basic hydrolysis can be used, such as sodium or lithium hydroxide in aq. ethanol, methanol or THF. When R_1 is Bn or PMB, standard hydrogenation can be used for the deprotection. These acid derivatives are within the scope of the instant invention and can be chemokine receptor modulators. The choice of R_1 is made depending on the availability of 4-2 or the stability of the piperidine R moiety and can be changed during the above sequence by suitable removal and re-esterification, such as hydrolysis of an ethyl ester (4-5 to 4-8, R_1 = Et) and replacement with a PMB ester (4-5 to 4-8, R_1 = PMB), using for example PMB-Cl in DMF with TEA as base, after the hydrogenation to 4-5 and 4-6 or 4-7 and 4-8.

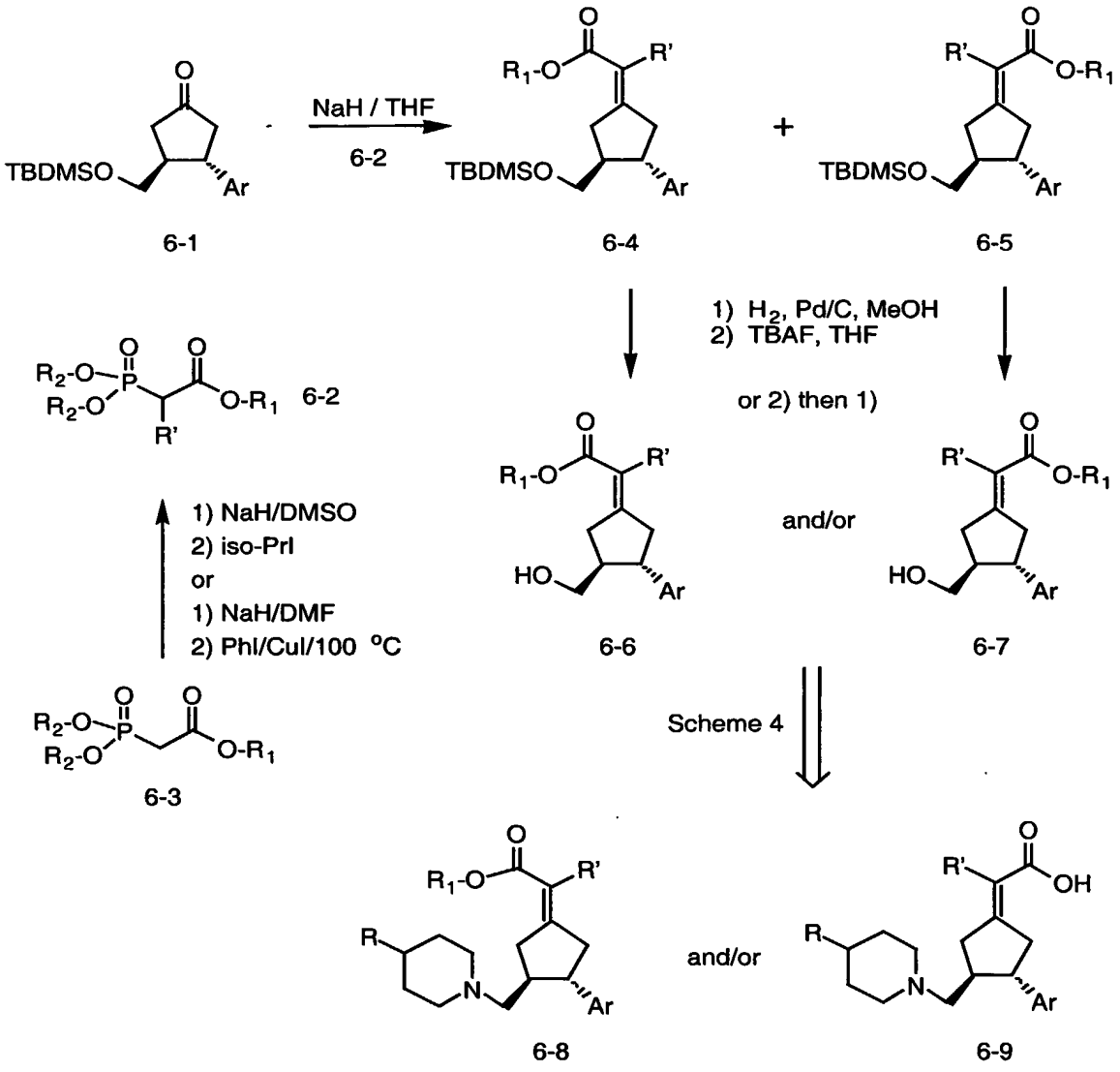
SCHEME 5



An alternative route for the preparation of some 1,3,4-trisubstituted cyclopentanes within the scope of the instant invention is given in Scheme 5. Alkylation of the acetic acid moiety of 5-1 (from Scheme 4, either as racemic or non-racemic and either as a single C-1 isomer or as a mixture) can be done under a variety of conditions with an appropriate alkylating agent, such as an alkyl or allyl halide or sulfonate, in the presence of a strong base, such as sodium hydride in DMF or KHMDS or LDA in THF at low temperature in the presence or absence of an anion stabilizer, such as HMPA, to give the 2 isomeric 2-alkyl acetic acid derivatives 5-2

and 5-3. Removal of the TBDMS group with TBAF (see Scheme 4) affords the alcohols 5-4 and 5-5 which may be separable by chromatographic methods. Oxidation to the aldehyde(s), reductive alkylation of a 4-substituted piperidine (see Schemes 12-29) and final removal of the acetic acid ester as described for Scheme 4 then affords the final product(s) 5-6 and/or 5-7. When an allyl derivative is used in the above alkylation, it can itself be a chemokine receptor modulator within the scope of the present invention or the double bond can be hydrogenated at the stage of 5-2 and 5-3 or 5-4 and 5-5 or at a point later in the sequence depending on the stability of the R and R_1 groups to various conditions.

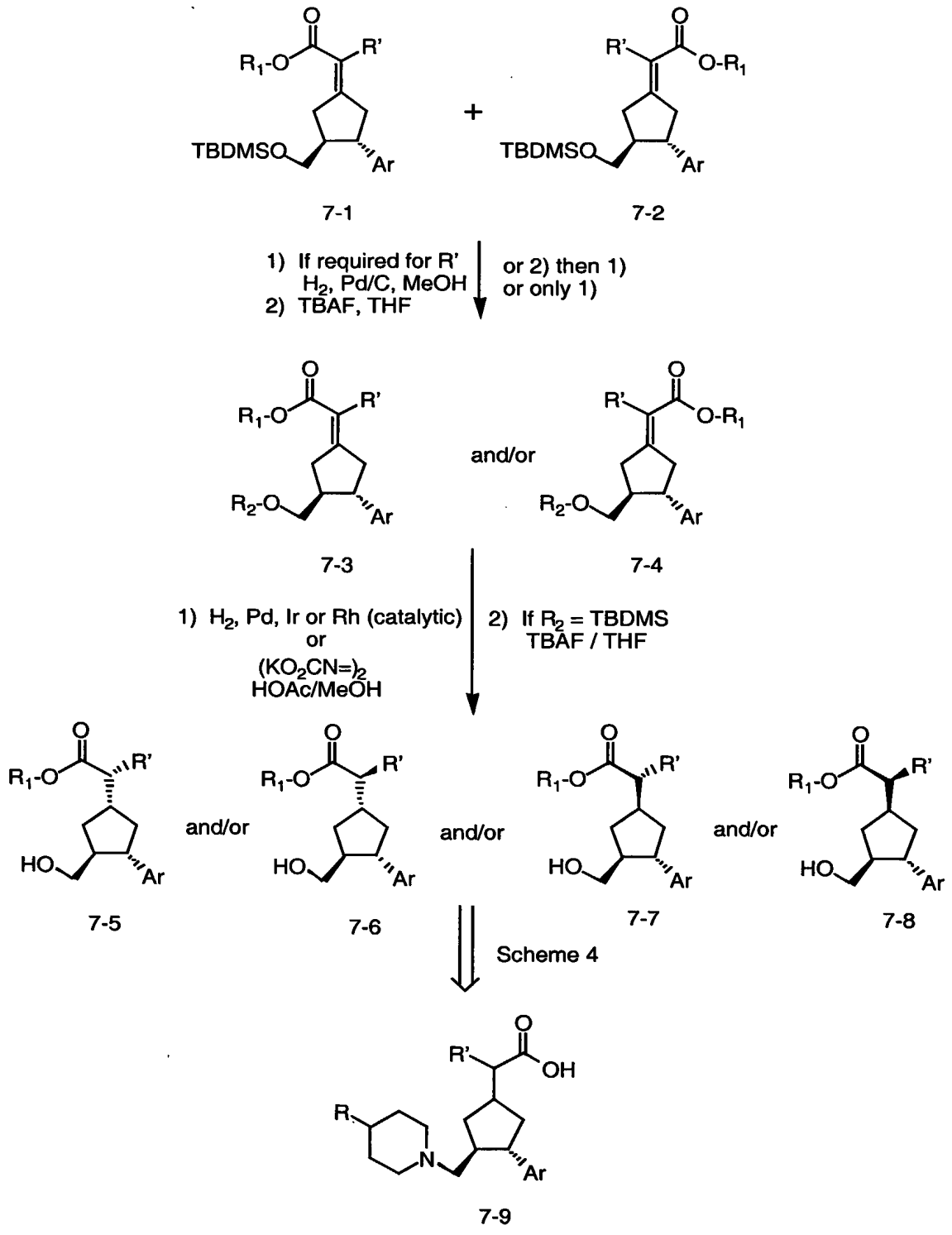
SCHEME 6



An alternative route for the preparation of some 1,3,4-trisubstituted cyclopentanes within the scope of the instant invention is given in Scheme 6. The ketone 6-1 (from Scheme 3) can be reacted with a 2-alkylsubstituted dialkylphosphonoacetic acid ester, such as 6-2 in which R' is Me, Et, cyclohexyl, iso-propyl, iso-butyl, cyclopropylmethyl, cyclobutylmethyl, etc. and fluoro to afford 6-4 and 6-5 which may be separable by chromatographic methods. When the desired dialkylphosphonoacetic acid ester is not commercially available, it can be prepared by alkylation of 6-3 under standard conditions, such as with an alkyl or allyl halide using

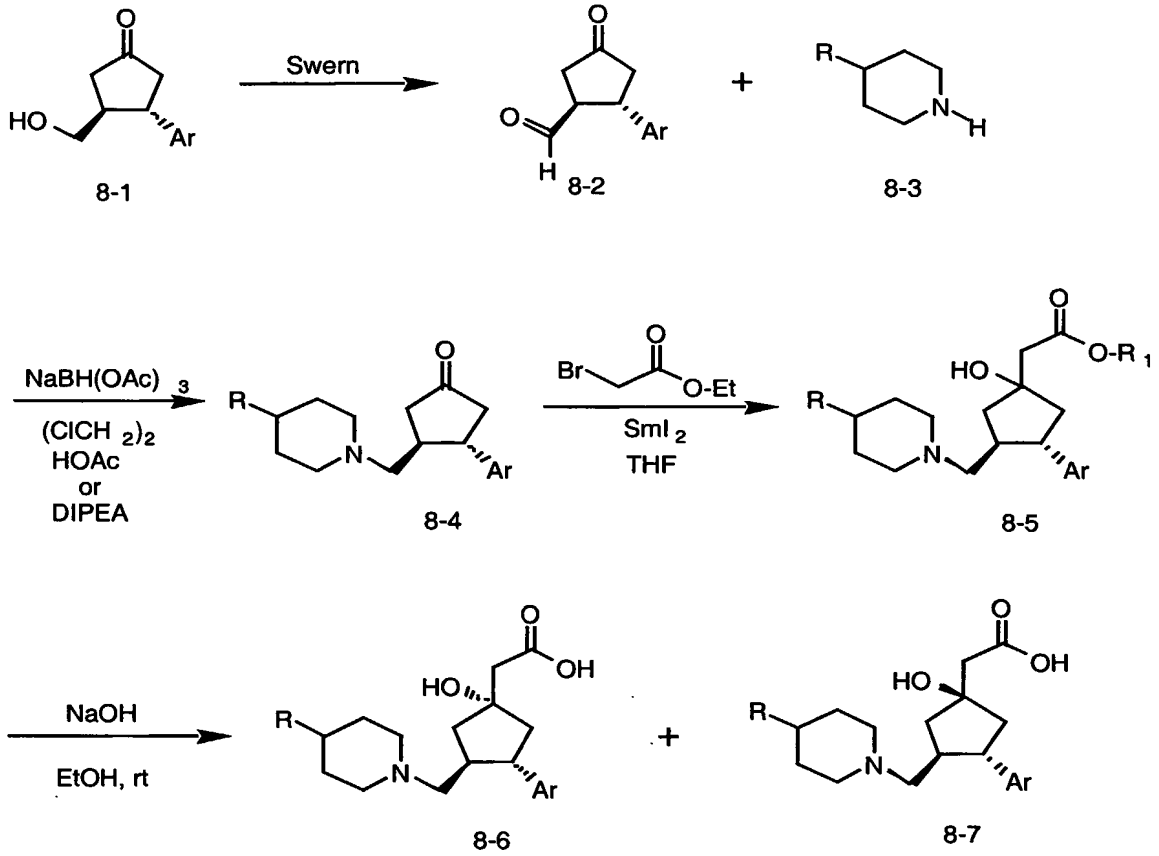
a strong base, such as sodium hydride or LHMDS, in a suitable solvent, such as DMF, THF or DMSO. Alternatively, 6-3 can be alkylated using sodium hydride as a base in DMF in the presence of CuI at 100 °C. The intermediate(s) 6-4 and/or 6-5 can be used as a mixture or may be separated by chromatography into a single double bond isomer at this point or after de-silylation to 6-6 and 6-7. These are then converted to the final product(s) 6-8 and/or 6-9 as described in Scheme 4. When R' in 6-2 contains a double bond, it can be selectively hydrogenated to the corresponding saturated compound, under standard conditions with 10% Pd/C in methanol, as 6-4 to 6-7 or further on in the sequence depending on the compatibility of R, R' and R_1.

SCHEME 7


R1-O
R'
TBDMSO
Ar
+
O-R1
7-1
7-2
1) If required for R'
H2, Pd/C, MeOH
2) TBAF, THF
or 2) then 1)
or only 1)
R2-O
and/or
7-3
7-4
1) H2, Pd, Ir or Rh (catalytic)
or
(KO2CN=)2
HOAc/MeOH
2) If R2 = TBDMS
TBAF / THF
HO
7-5
7-6
7-7
7-8
Scheme 4
OH
R
N
7-9

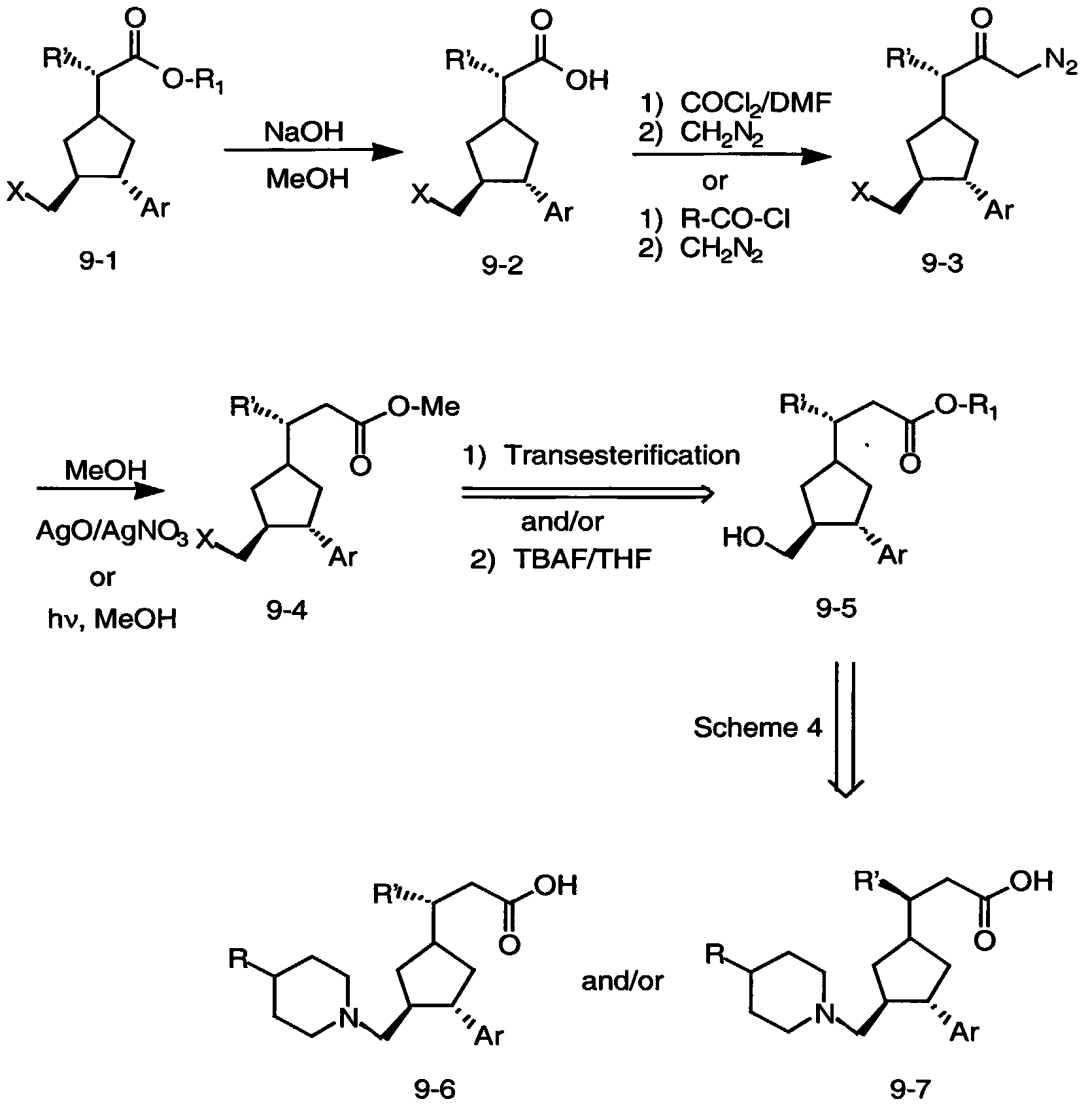
An alternative route for the preparation of some 1,3,4-trisubstituted cyclopentanes within the scope of the instant invention is given in Scheme 7. The TBDMS ethers 7-1 and/or 7-2 (from Scheme 6, either separate or as a mixture) can be desilylated with TBAF (see Scheme 4) to afford the alcohols 7-3 and/or 7-4. When R' contains unsaturation, this can be selectively hydrogenated either prior to or following the desilylation, depending on the best point of separation and the stability of the TBDMS group. The C-1 exo-methylene unsaturation can be hydrogenated either catalytically under standard conditions with Pd (R_2 = TBDMS) or alcohol directed conditions with Ir or Rh (R_2 = H) (see Scheme 4) or with chemical reduction, such as with potassium azodicarboxylate in the presence of acetic acid in methanol, to afford the 4 possible stereoisomers 7-5 to 7-8. These isomers may be separable at this step or later in the sequence. The choice of catalyst and whether the reduction is done on the TBDMS ether or alcohol can alter the ratio of C-1 epimeric products obtained as described in Scheme 4 and can be used to preferentially obtain the desired isomer(s). These are then converted to the final product(s) 7-9 as described in Scheme 4. When R' contains a double bond, it can be selectively hydrogenated as above in a separate reaction or simultaneously with the reduction of the C-1 exo-methylene to the corresponding saturated compounds 7-5 to 7-8.

SCHEME 8



An alternative route for the preparation of some 1,3,4-trisubstituted cyclopentanes within the scope of the instant invention is given in Scheme 8. The alcohol 8-1 (from Scheme 3) can be oxidized to the aldehyde 8-2 under a variety of methods (see Scheme 4), such as Swern conditions. Selective reductive alkylation of a 4-substituted piperidine 8-3 with the aldehyde of 8-2 using for example sodium triacetoxyborohydride or sodium cyanoborohydride in a suitable solvent, such as methylene chloride, methanol or 1,2-dichloroethane, affords the ketone product 8-4. Addition of acetate to the ketone, such as in the free radical addition of ethyl bromoacetate in the presence of SmI_2 in THF, gives a mixture of the C-1 alcohols 8-5. Careful hydrolysis of the ethyl ester afforded the separable acids 8-6 and 8-7 which are within the scope of the present invention and which can be chemokine receptor modifiers.

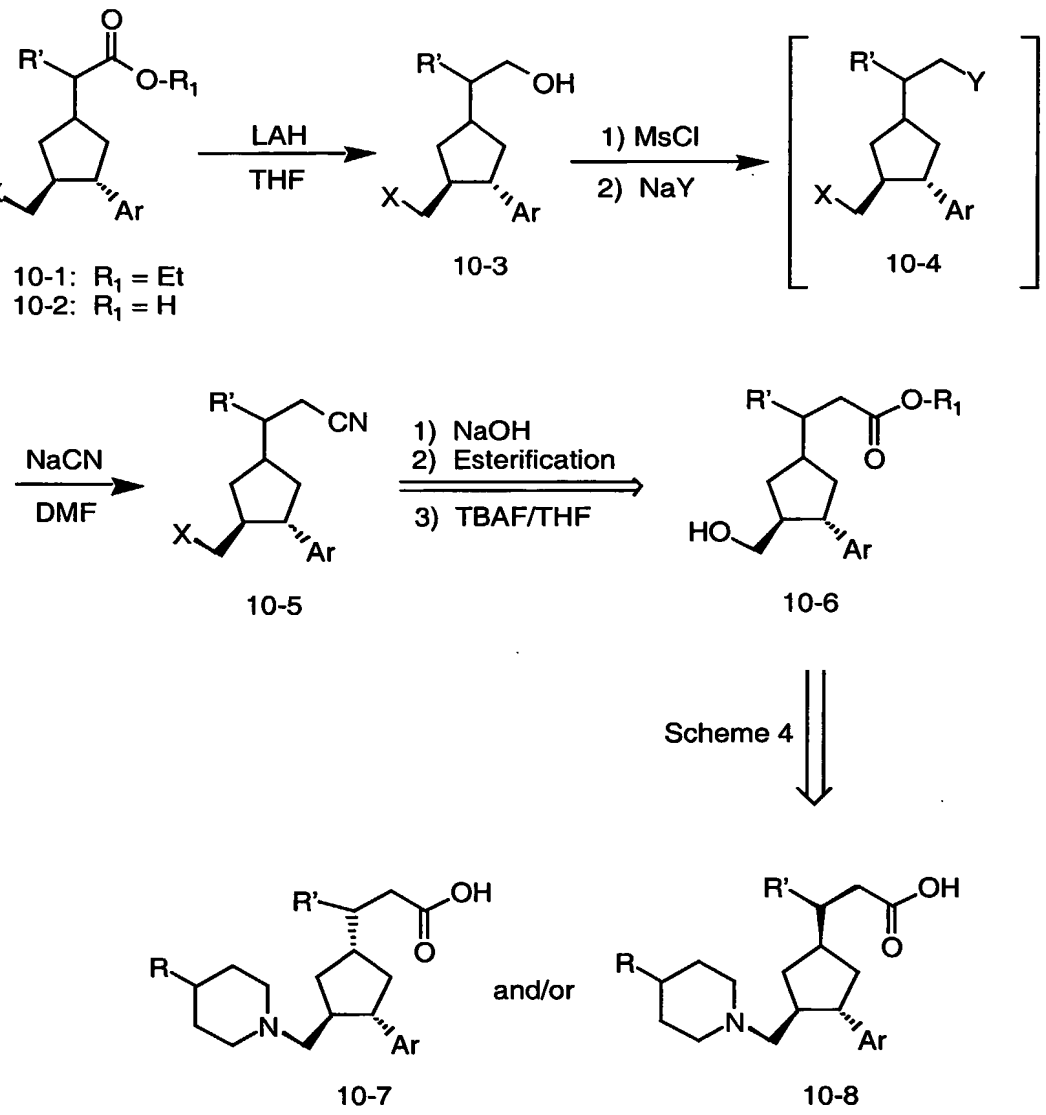
SCHEME 9



An alternative route for the preparation of some 1,3,4-trisubstituted cyclopentanes within the scope of the instant invention is given in Scheme 9 in which the C-1 acetic acid moiety can be homolygated. The ester 9-1 (from Scheme 5 or 7, X = OTBDMS or other suitably protected alcohol group) can be hydrolyzed under standard conditions, such as sodium hydroxide in aq. methanol, to the acid 9-2. A standard Arndt-Eistert reaction can be used to homolygate the acetic acid to a propionic acid. Thus, the acid can be activated as an acid chloride, for example with oxalyl chloride in the presence of a catalytic amount of DMF in methylene chloride, or as a mixed anhydride with iso-butyl chloroformate or pivaloyl chloride in

methylene chloride. Subsequent reaction with diazomethane in an inert solvent, such as ether or methylene chloride, affords the diazoketone 9-3 which can be decomposed in methanol in the presence of silver oxide and/or silver nitrate or with irradiation in methanol to give the methyl ester 9-4. If required for conversion to the desired final product, hydrolysis of the methyl ester and reesterification can give a more compatible ester as detailed in the above schemes. Subsequent removal of the silyl ether (or other suitable alcohol protecting group) leads to the alcohol 9-5 which can be converted to the final product(s) 9-6 and/or 9-7 as detailed in Scheme 4. Alternatively, if the piperidine 4-R group in the final product is compatible with the above homolygations, X in 9-1 can be the already functionalized piperidine moiety as obtained in Schemes 4, 5 and 7 above.

SCHEME 10

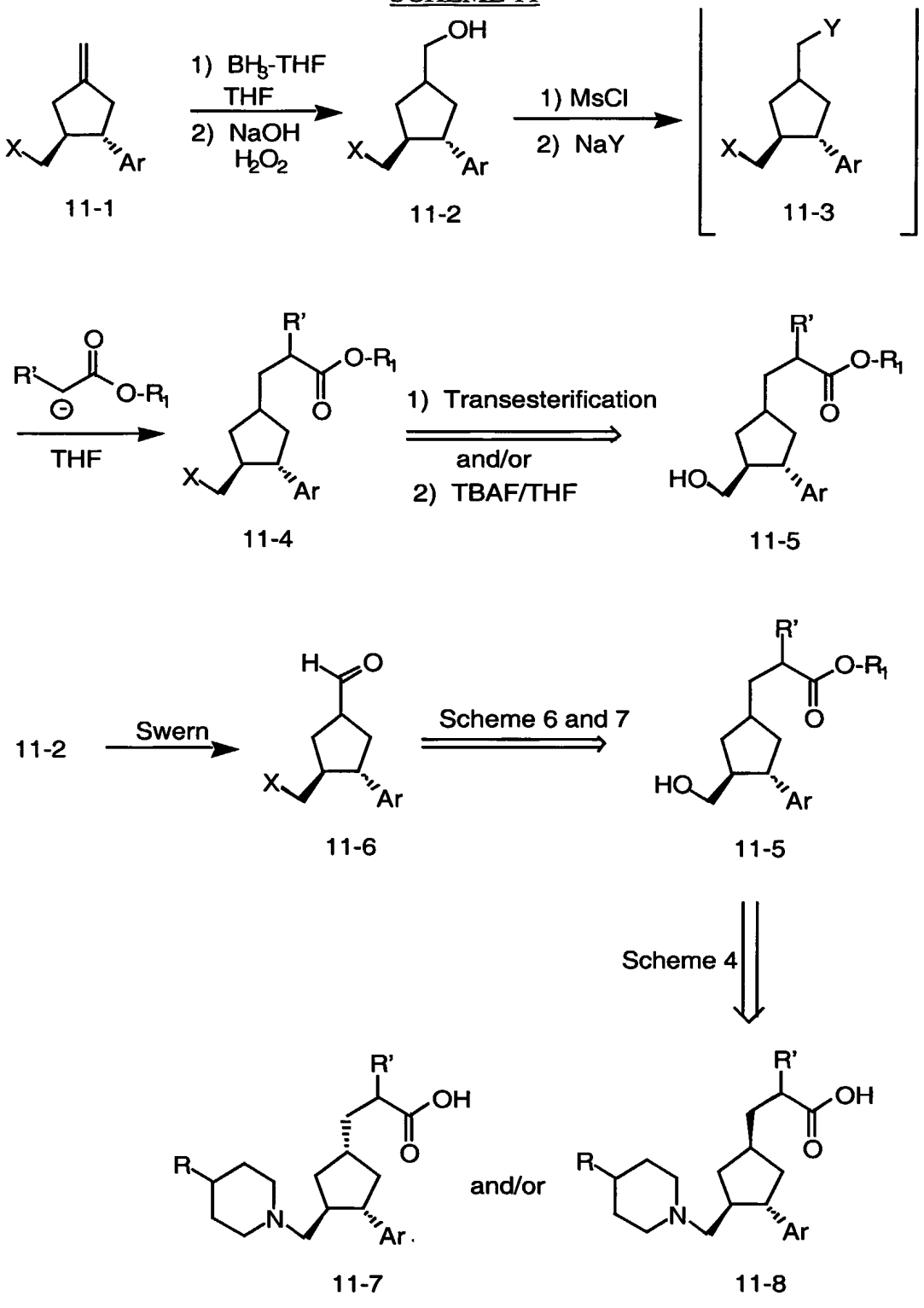


An alternative route for the preparation of some 1,3,4-trisubstituted cyclopentanes within the scope of the instant invention in which the C-1 acetic acid moiety can be homolygated is given in Scheme 10. The homolygation can be achieved through reduction of either the ester 10-1 or acid 10-2 (from Scheme 5 or 7, X = OTBDMS or other suitably protected alcohol group) with an appropriate reducing agent, such as LAH in THF, to give the alcohol 10-3. Activation of the alcohol as its mesylate and/or the bromide or iodide 10-4 followed by displacement with sodium cyanide would afford the nitrile 10-5. Hydrolysis to the acid, esterification and removal of the C-3 hydroxymethyl protecting group would led to the hydroxymethyl

intermediate 10-6 which can be converted to the final product(s) 10-7 and/or 10-8 as detailed in Scheme 4. Alternatively, if the 4-R group in the final product piperidine is compatible with the above homolygations, X in 10-2 can be the already functionalized piperidine moiety as obtained in Schemes 4, 5 and 7 above.

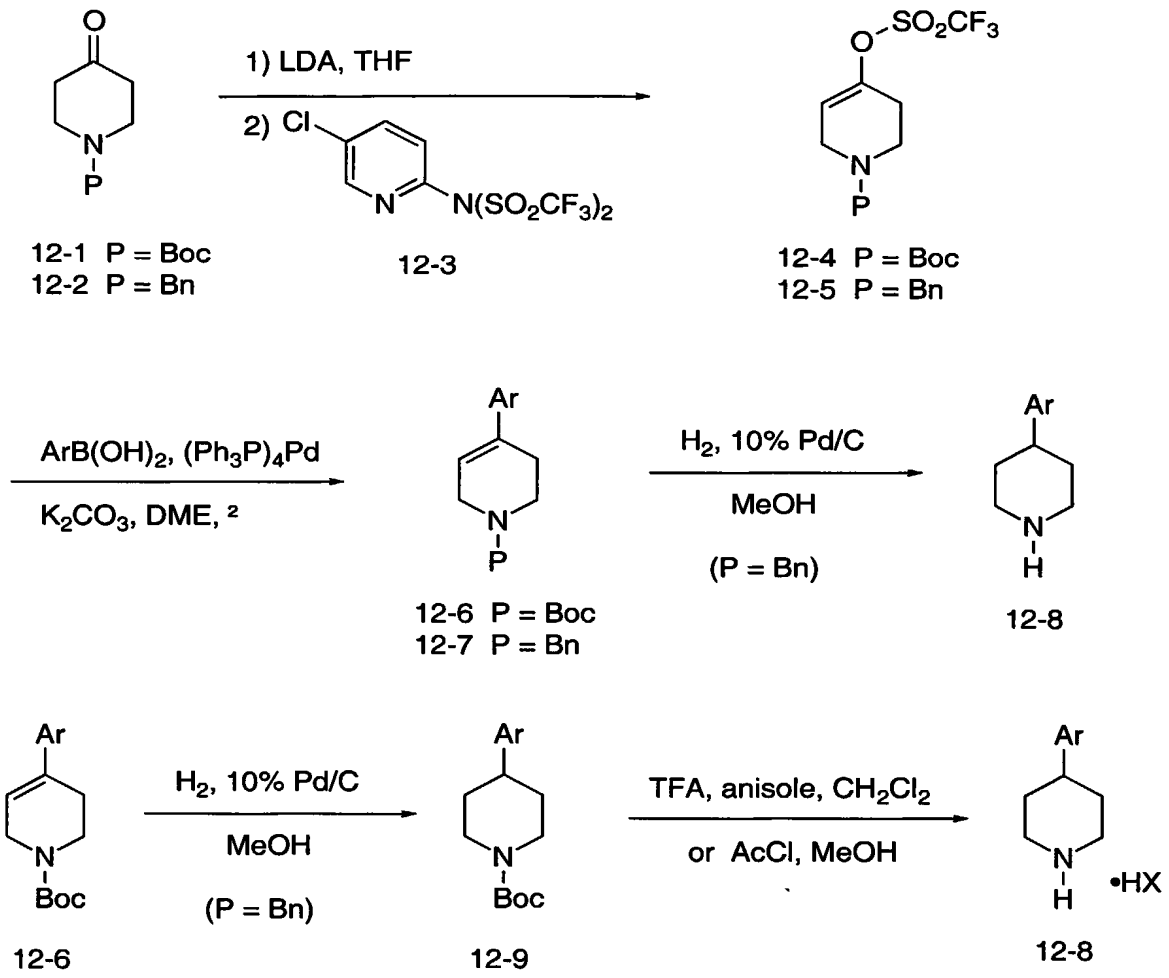
5

SCHEME 11


1) BH3-THF
THF
2) NaOH
H2O2
1) MsCl
2) NaY
11-1
11-2
11-3
THF
1) Transesterification
and/or
2) TBAF/THF
11-4
11-5
Swern
Scheme 6 and 7
11-2
11-6
11-5
Scheme 4
and/or
11-7
11-8

An alternative route for the preparation of some 1,3,4-trisubstituted cyclopentanes within the scope of the instant invention in which the C-1 acetic acid moiety can be homolygated is given in Scheme 11. Standard hydroboration of 11-1 (Scheme 3, X = OTBDMS or other suitably protected alcohol group), such as with borane-THF complex in THF followed by an oxidative work-up with NaOH and hydrogen peroxide or trimethylamine-N-oxide, affords the alcohol 11-2. Activation of alcohol 11-2 as the mesylate and/or bromo or iodo 11-3 and displacement with an acetate anion gives the ester 11-4 in which the R' is now on the β carbon from the cyclopentane ring. Transesterification, if necessary, followed by deprotection at C-3 leads to 11-5. Alternatively, oxidation of 11-2, such as with the Swern method, gives the aldehyde 11-6 which can be elaborated to 11-5 as shown in Schemes 4-7. The hydroxymethyl intermediate 11-5 can be converted to the final product(s) 11-7 and/or 11-8 as detailed in Scheme 4. Alternatively, if the 4-R group in the final product piperidine is compatible with the above homolygations, X in 10-2 can be the already functionalized piperidine moiety as obtained in Schemes 4, 5 and 7 above.

SCHEME 12



12-1 P = Boc
12-2 P = Bn

12-3

12-4 P = Boc
12-5 P = Bn

12-6 P = Boc
12-7 P = Bn

12-8

12-6

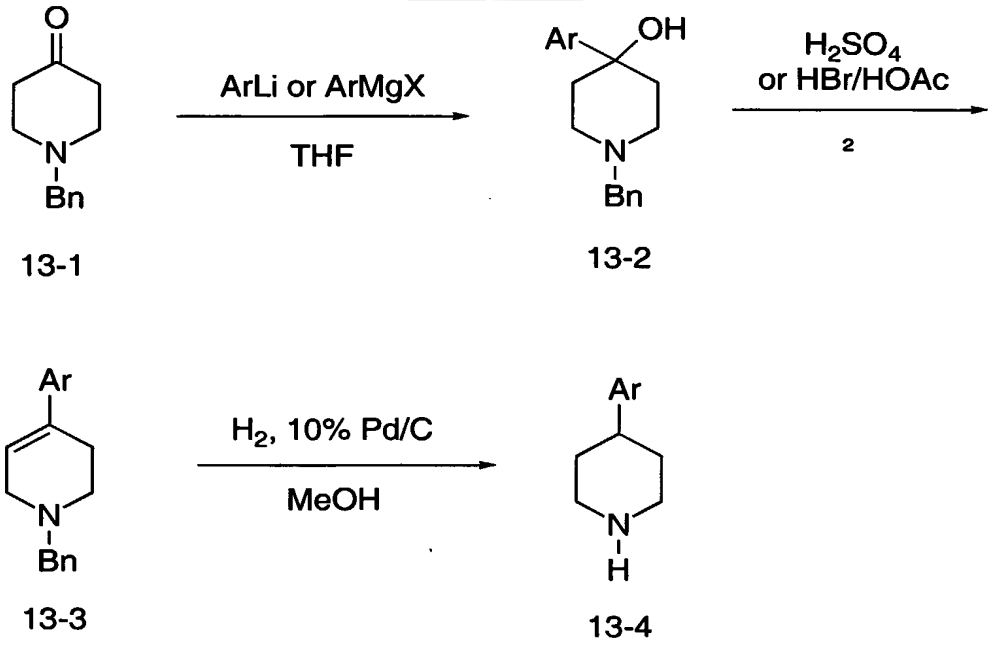
12-9

12-8

One method of generating 4-aryl piperidines as intermediates is given in Scheme 12. Reaction of commercially available 12-1 or 12-2 with a strong base, such as LDA, LiHDMS, NaHMDS, KHMDS, or NaH followed by treating with a suitable triflating agent, such as 5-chloropyrid-2-yl triflimide (12-3), N-phenyl triflimide or triflic anhydride, provides enol triflates 12-4 or 12-5. Heating with commercially available aryl boronic acids in the presence of a suitable palladium(0) catalyst such as tetrakis triphenylphosphine palladium, a base (such as potassium carbonate or sodium carbonate), in a solvent such as DME, THF, dioxane or toluene/ethanol, effects coupling to provide the unsaturated products 12-6 or 12-7. In the case of 12-7, treatment with a heterogeneous palladium catalyst in methanol or ethanol in an atmosphere of hydrogen provides the desired intermediate 12-8.

Alternatively, the Boc protected derivative 12-6 is hydrogenated under standard conditions to provided the saturated piperidine 12-9, which is then deprotected under acidic conditions (such as trifluoroacetic acid and anisole in methylene chloride or HCl in methanol), to provide 12-8 as a salt, which is then utilized as the cyclic secondary amine component as shown above in Schemes 4, 5, 6, 7, 8, 9, 10 and 11.

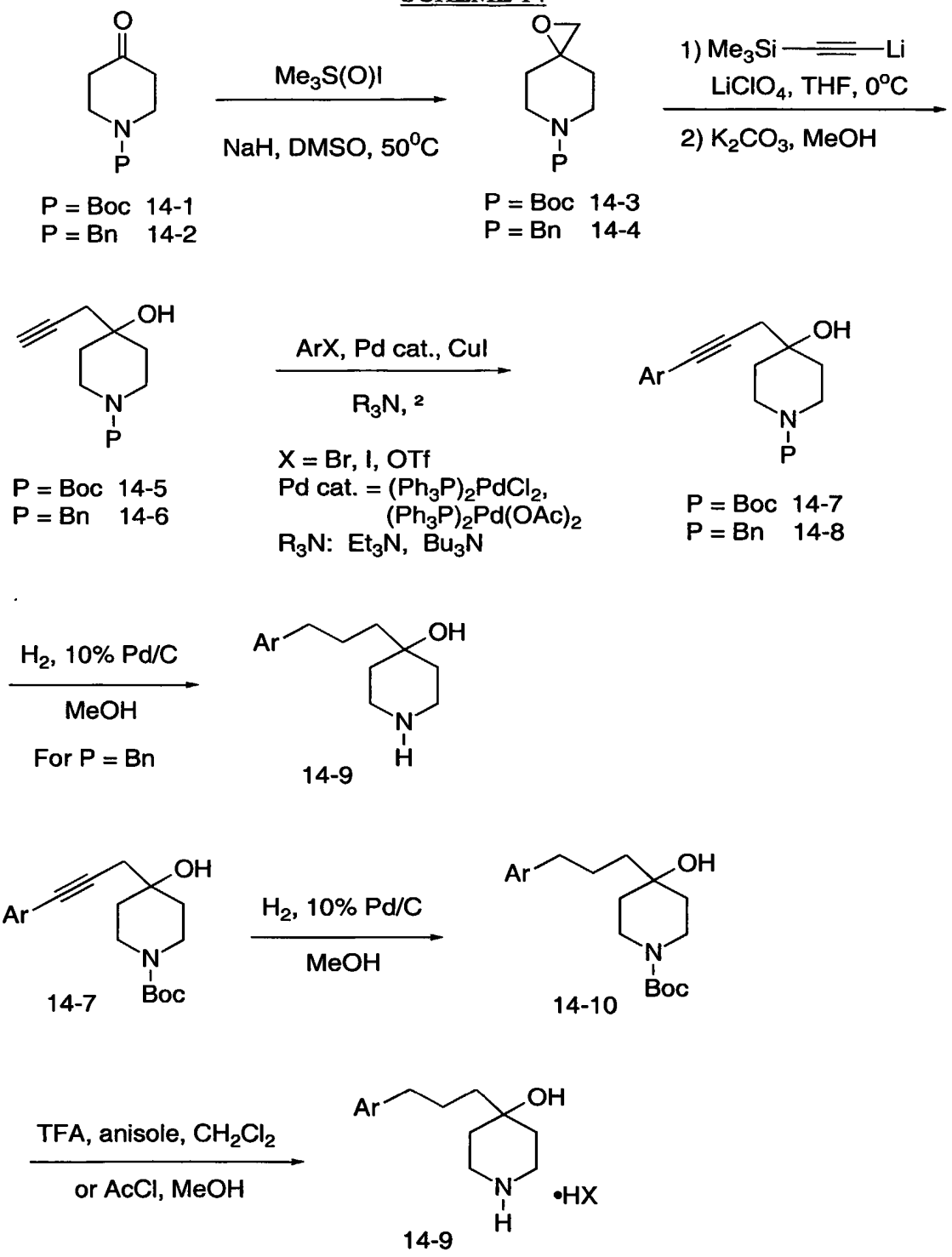
SCHEME 13



An alternative method of generating 4-aryl piperidines as intermediates is given in Scheme 13. Reaction of commercially available 13-1 with an aryl magnesium halide or with an aryllithium (in the presence or absence of anhydrous cerium trichloride) provides tertiary alcohol 13-2, which upon treatment under acidic conditions (such as sulfuric acid, HBr in acetic acid, HCl in acetic acid) or under dehydrating conditions (such as with thionyl chloride in pyridine or with phosphorus oxychloride) provides olefin 13-3. Hydrogenation under standard conditions using either hydrogen gas or a hydrogen donor (such as ammonium formate or cyclohexene) effects reduction of the double bond and cleavage of the N-benzyl group to provide the desired intermediate 13-4. Under some circumstances it may be preferable to reduce the double bond under non-hydrogenolytic conditions, for example with triethylsilane and trifluoroacetic acid or under dissolving metal conditions (for

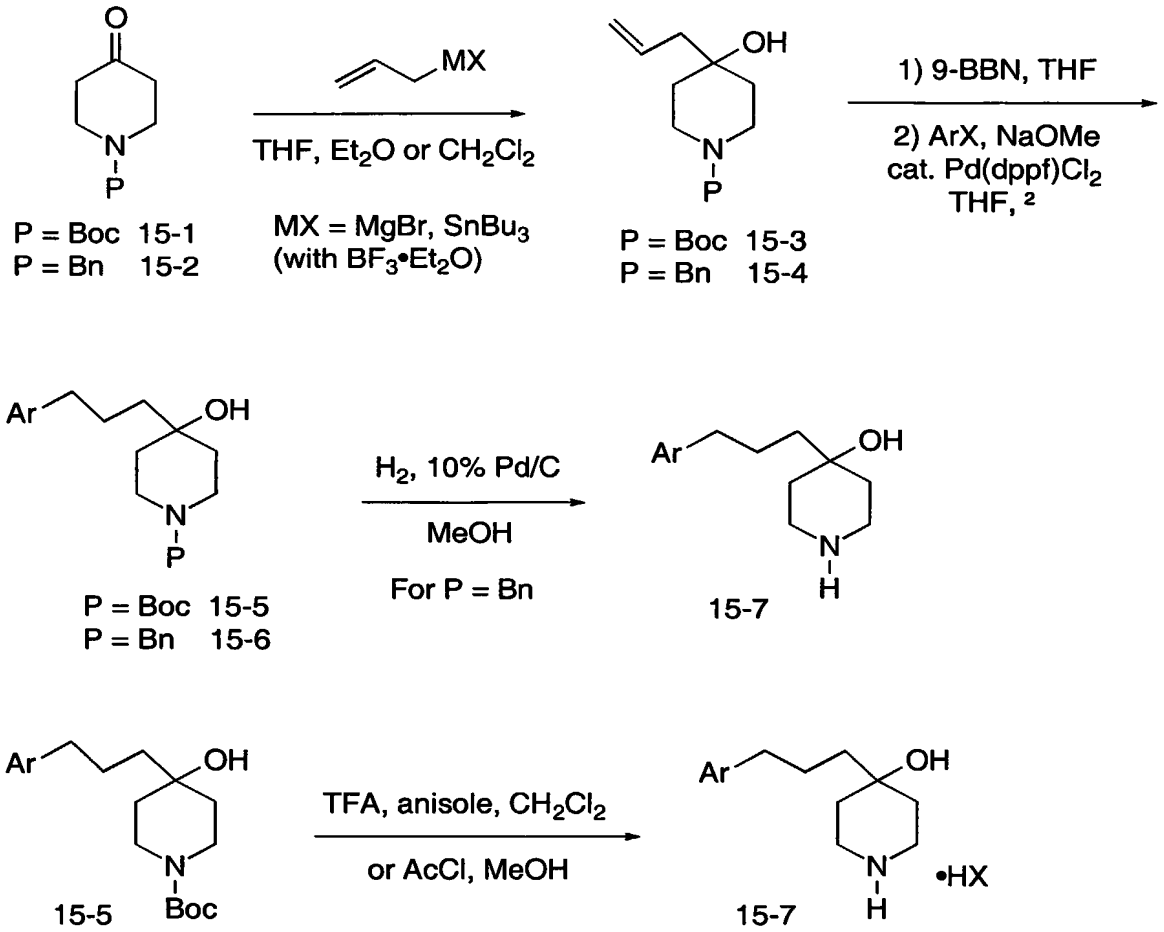
example, sodium or lithium metal in ammonia or a lower alkyl amine). If the N-benzyl group is not removed under these conditions, it may be cleaved by treatment with either vinyl chloroformate and then hydrogen chloride or by treatment with 2-chloroethyl chloroformate followed by heating in methanol. The product 13-4 is then utilized as the cyclic secondary amine component as shown above in Schemes 4, 5, 6, 7, 8, 9, 10 and 11.

SCHEME 14


Me3S(O)I
NaH, DMSO, 50°C
1) Me3Si—≡—Li
LiClO4, THF, 0°C
2) K2CO3, MeOH
P = Boc 14-1
P = Bn 14-2
P = Boc 14-3
P = Bn 14-4
ArX, Pd cat., CuI
R3N, ²
X = Br, I, OTf
Pd cat. = (Ph3P)2PdCl2,
(Ph3P)2Pd(OAc)2
R3N: Et3N, Bu3N
P = Boc 14-5
P = Bn 14-6
P = Boc 14-7
P = Bn 14-8
H2, 10% Pd/C
MeOH
For P = Bn
14-9
14-7
14-10
TFA, anisole, CH2Cl2
or AcCl, MeOH
•HX

One route for the preparation of 4-hydroxy-4-(3-arylpropyl)piperidines is given in Scheme 14. Treatment of commercially available 4-piperidones 14-1 or 14-2 with trimethylsulfonium iodide and sodium hydride in dimethyl sulfoxide at or above room temperature provides spiro epoxides 14-3 or 14-4. Addition of the lithium salt of trimethylsilylacetylene to these epoxides in the presence of lithium perchlorate in THF at 0 degrees C, followed by treatment of the crude intermediate with potassium carbonate in methanol, affords the acetylenic alcohols 14-5 or 14-6. Heating of these alkynes with an aromatic halide or triflate in the presence of copper(I) iodide, a palladium catalyst such as bis(triphenylphosphine)palladium dichloride or bis(triphenylphosphine)palladium diacetate in the presence of a tertiary amine base such as triethylamine or tributylamine, then provides coupling products 14-7 or 14-8. In the case of the N-benzyl protected intermediate 14-8, hydrogenation/hydrogenolysis under standard conditions (for example 10% Pd/C in an atmosphere of hydrogen) provides desired intermediate 14-9. For the Boc protected species 14-7, hydrogenation as above provides the saturated piperidine 14-10, and treatment of this compound under anhydrous acidic conditions (for example, trifluoroacetic acid and anisole in methylene chloride, or acetyl chloride in methanol) then yields the salt of intermediate 14-9. This compound is then utilized as the cyclic secondary amine component as shown above in Schemes 4, 5, 6, 7, 8, 9, 10 and 11. Alternatively, if 4-piperidone is attached directly to the functionalized alkylcyclopentane framework described above and no functionality in the alkylcyclopentane would be affected, then the chemistry described herein can be carried out treating the aforementioned alkylcyclopentane segment as 'P' given in Scheme 14.

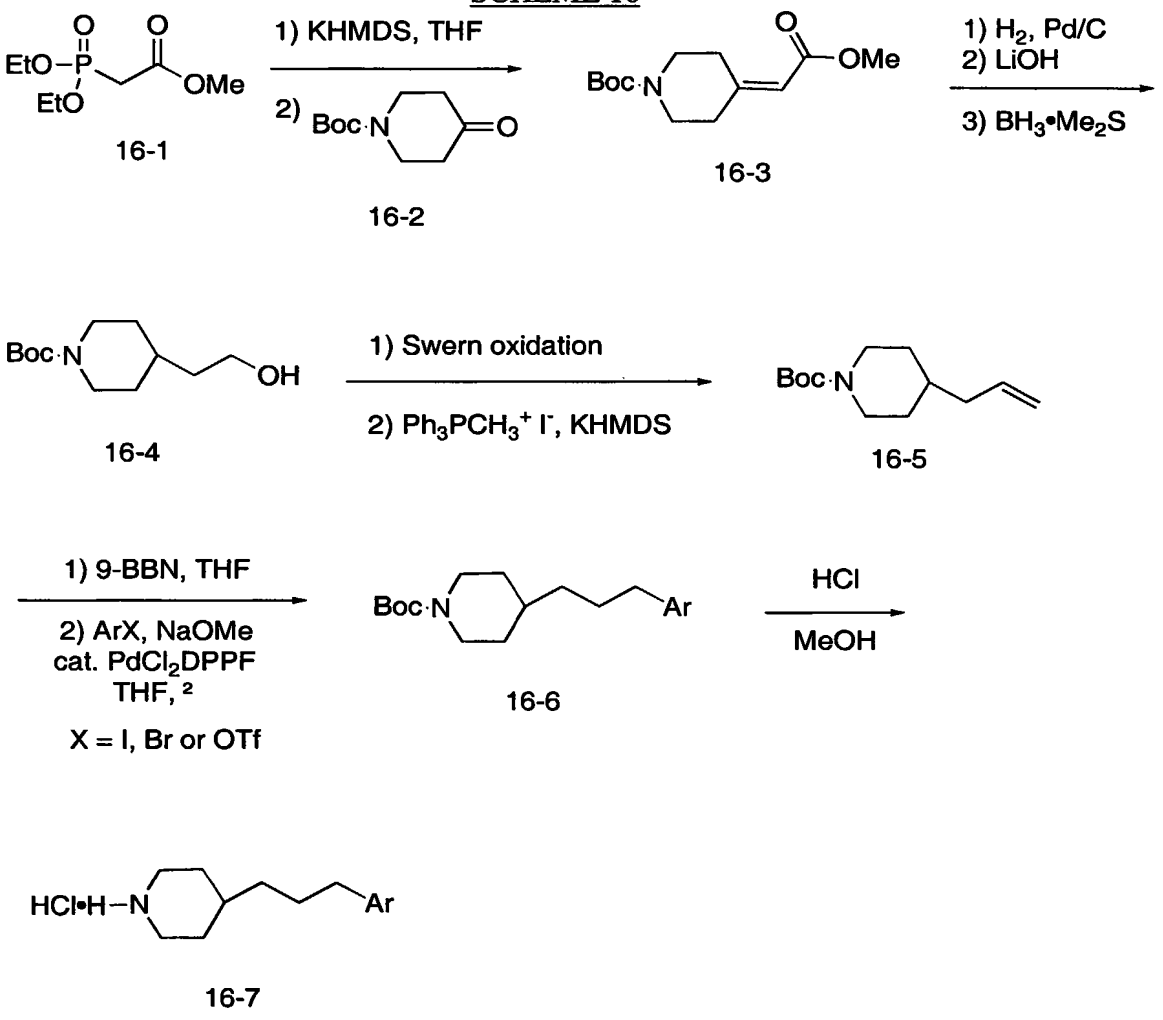
SCHEME 15



An alternative route for the preparation of 4-hydroxy-4-(3-arylpropyl)piperidines is given in Scheme 15. Treatment of commercially available 4-piperidones 15-1 or 15-2 with a suitable allyl metal compound (such as allylmagnesium bromide or allyltributylstannane (in the presence of boron trifluoride etherate) in THF, ether or dichloromethane, provides adducts 15-3 or 15-4. Hydroboration with a dialkylborane, such as 9-borabicyclo[3.3.1]nonane (9-BBN), followed by treatment with an aryl halide (the halides preferably being bromide or iodide) or aryl triflate and sodium methoxide in the presence of a suitable soluble palladium catalyst, for example $Pd(dppf)Cl_2$, in warm to refluxing THF, provides the 3-arylpropyl derivatives 15-5 and 15-6. For benzylamine 15-6, hydrogenolysis under standard conditions provides the desired intermediate 15-7. For Boc substituted piperidine 15-5, exposure to suitable anhydrous acidic conditions (for example trifluoroacetic acid and anisole in methylene chloride or HCl in methanol at

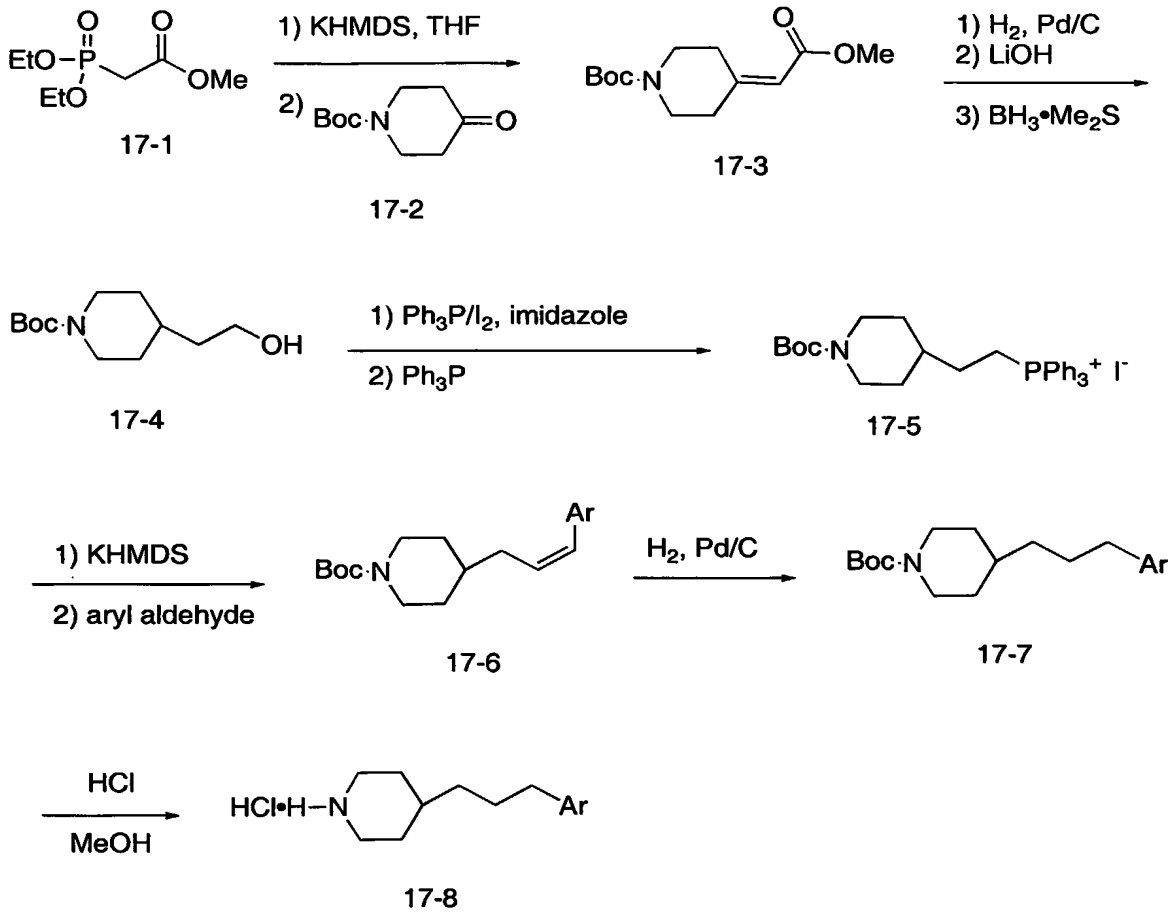
temperatures from 0-25 degrees C) affords the salt of 15-7. This compound is then utilized as the cyclic secondary amine component as shown above in Schemes 4, 5, 6, 7, 8, 9, 10 and 11. Alternatively, if no functionality are present in the alkylcyclopentane framework that would be adversely effected by the above mentioned chemistry, then 4-piperidone may be attached directly to the alkylcyclopentane framework described above, and the chemistry described in this paragraph can be carried out equating the alkylcyclopentane segment to the group 'P' given in Scheme 15, structures 1 through 6.

SCHEME 16



A route for the preparation of 4-(3-arylpropyl)piperidines is given in Scheme 16. Treatment of phosphonoacetate 16-1 with KHMDS followed by addition of commercially available N-Boc -4-piperidone 16-2 provides unsaturated ester 16-3. Hydrogenation of 16-3 followed by hydrolysis to the acid and then reduction with borane•methyl sulfide then affords primary alcohol 16-4. Mild oxidation of 16-4 under Swern conditions provides the corresponding aldehyde, which upon treatment with the Wittig reagent prepared from methyltriphenylphosphonium iodide and KHMDS yields olefin 16-5. Hydroboration with a dialkylborane, such as 9-borabicyclo[3.3.1]nonane (9-BBN), followed by treatment with an aryl halide (the halides preferably being bromide or iodide) or aryl triflate in the presence of a suitable soluble palladium catalyst, for example $PdCl_2DPPF$, in warm to refluxing THF, provides the 3-arylpropyl derivative 16-6. Removal of the Boc group under acidic conditions, for example with HCl in methanol or with trifluoroacetic acid in methylene chloride, then affords the 1-unsubstituted piperidine 16-7, which can then be employed as the secondary amine component in the syntheses described above in Schemes 4, 5, 6, 7, 8, 9, 10 and 11.

SCHEME 17

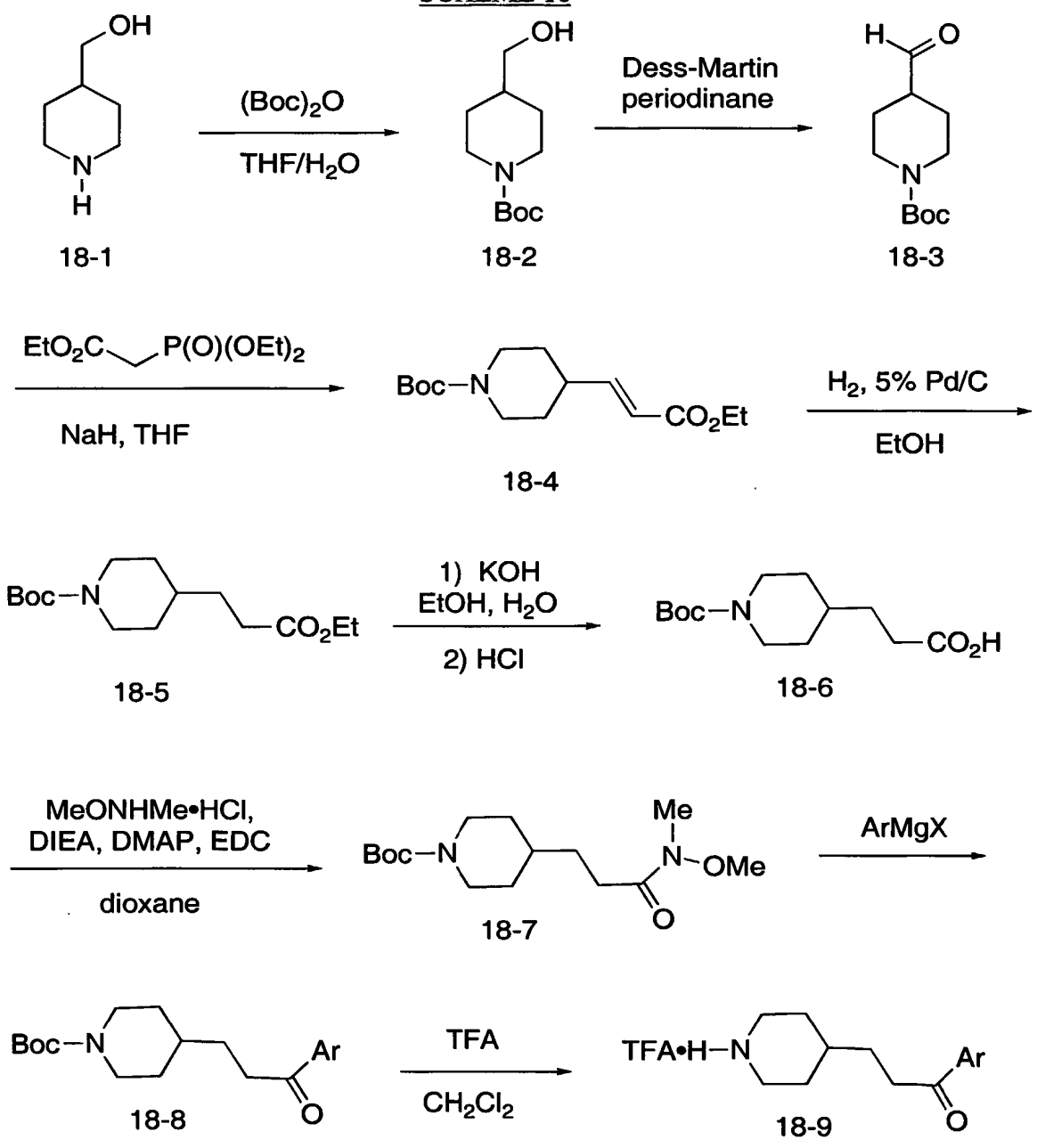


17-1 17-2 17-3 17-4 17-5 17-6 17-7 17-8

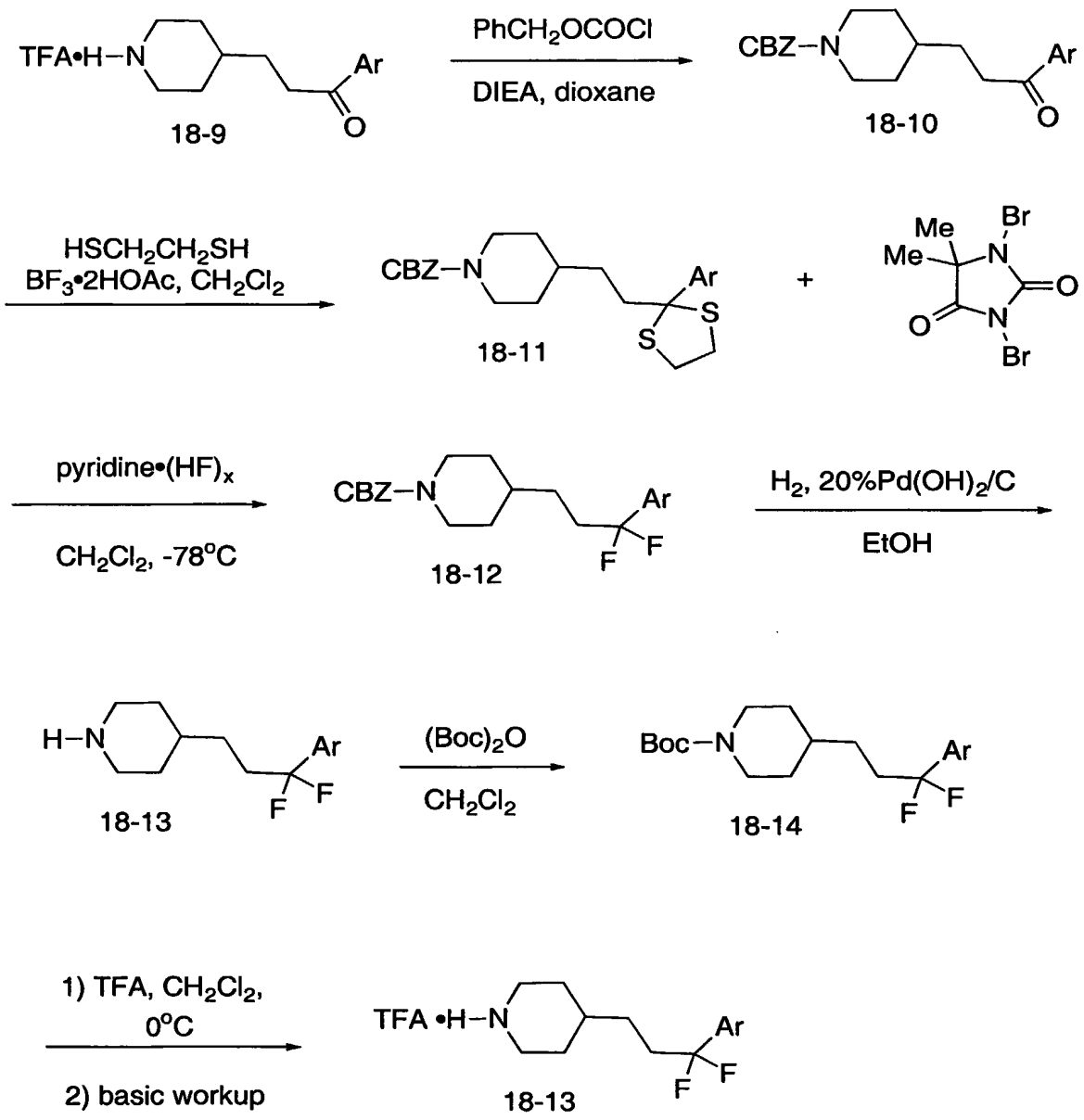
Another route for the preparation of 4-(3-arylpropyl)piperidines is given in Scheme 17. Treatment of phosphonoacetate 17-1 with KHMDS followed by addition of commercially available N-Boc -4-piperidone 17-2 provides unsaturated ester 17-3. Hydrogenation of 17-3 followed by hydrolysis to the acid and then reduction with borane•methyl sulfide then affords primary alcohol 17-4. Formation of the alkyl iodide with triphenylphosphine and iodine in the presence of imidazole followed by treatment with triphenylphosphine provides phosphonium salt 17-5. Deprotonation with a suitable base, for example, KHMDS, LiHMDS, NaHMDS, NaH, LDA, or KH affords the Wittig agent *in situ*, which upon treatment with a suitable aromatic aldehyde yields the unsaturated derivative 17-6. Hydrogenation under standard conditions provides 17-7, and removal of the Boc group with HCl in methanol or with other acidic conditions then provides the 1-unsubstituted piperidine

17-8, which can then be employed as the secondary amine component in the syntheses described above in Schemes 4, 5, 6, 7, 8, 9, 10 and 11.

SCHEME 18



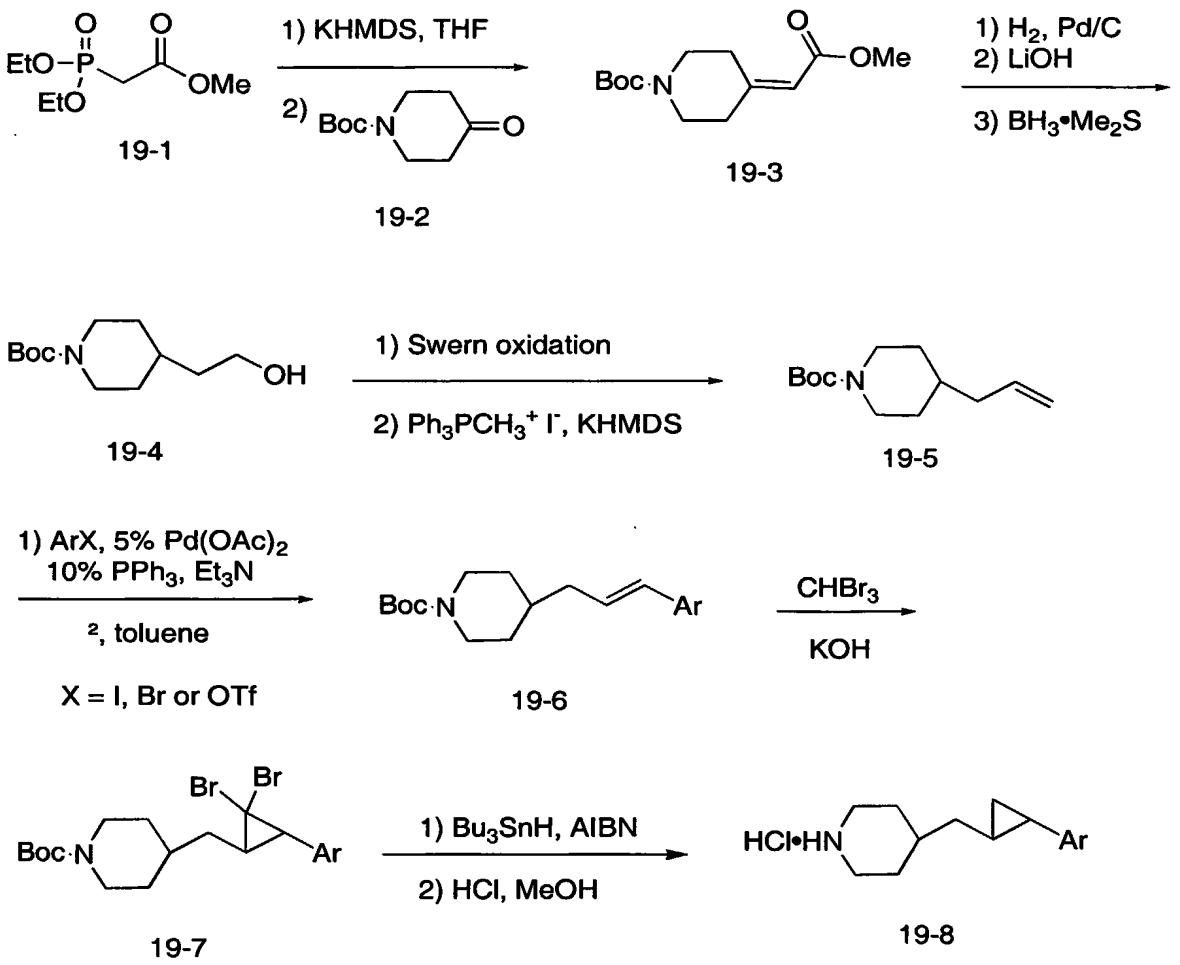
SCHEME 18, con't.



5 Preparation of piperidines with a 4-(3-aryl-3,3,-difluoropropyl) side chain is given in Scheme 18. Treatment of commercially available 18-1 with Boc anhydride provides protected piperidine 18-2. Oxidation, for example with the Dess-Martin reagent, by a Swern oxidation, or other known methods provides aldehyde 18-3. Condensation under Horner-Wadsworth-Emmons conditions affords unsaturated ester 18-4, which

is hydrogenated to ester 18-5 and then hydrolysed to acid 18-6. Formation of the N-methyl-N-methoxy amide 18-7 is carried out employing standard activating agents such as EDC. Weinreb amide 18-7 is then allowed to react with an arylmetal reagent, such as an aryl magnesium halide or an aryllithium, to provide ketone 18-8. Cleavage of the protecting Boc group under acidic conditions yields 18-9, which is reprotected with a carbobenzyloxy group under standard conditions, to afford 18-10. Formation of dithiolane 18-11 with ethanedithiol and boron trifluoride is followed by treatment with 1,3-dibromo-3,3-dimethylhydantoin and pyridine-hydrogen fluoride complex at or around -78 degrees C, to provide gem-difluoro derivative 18-12. Removal of the CBZ group under reductive conditions provides piperidine 18-13, which may be employed directly as the secondary amine in chemistry described above. Alternatively, if additional purification is desired, 18-13 may be protected with a Boc group to afford 18-14. After suitable purification, the Boc group is removed under acidic conditions at or near 0 degrees C. A controlled, basic work-up then provides 18-13, suitable for use as described above in Schemes 4, 5, 6, 7, 8, 9, 10 and 11.

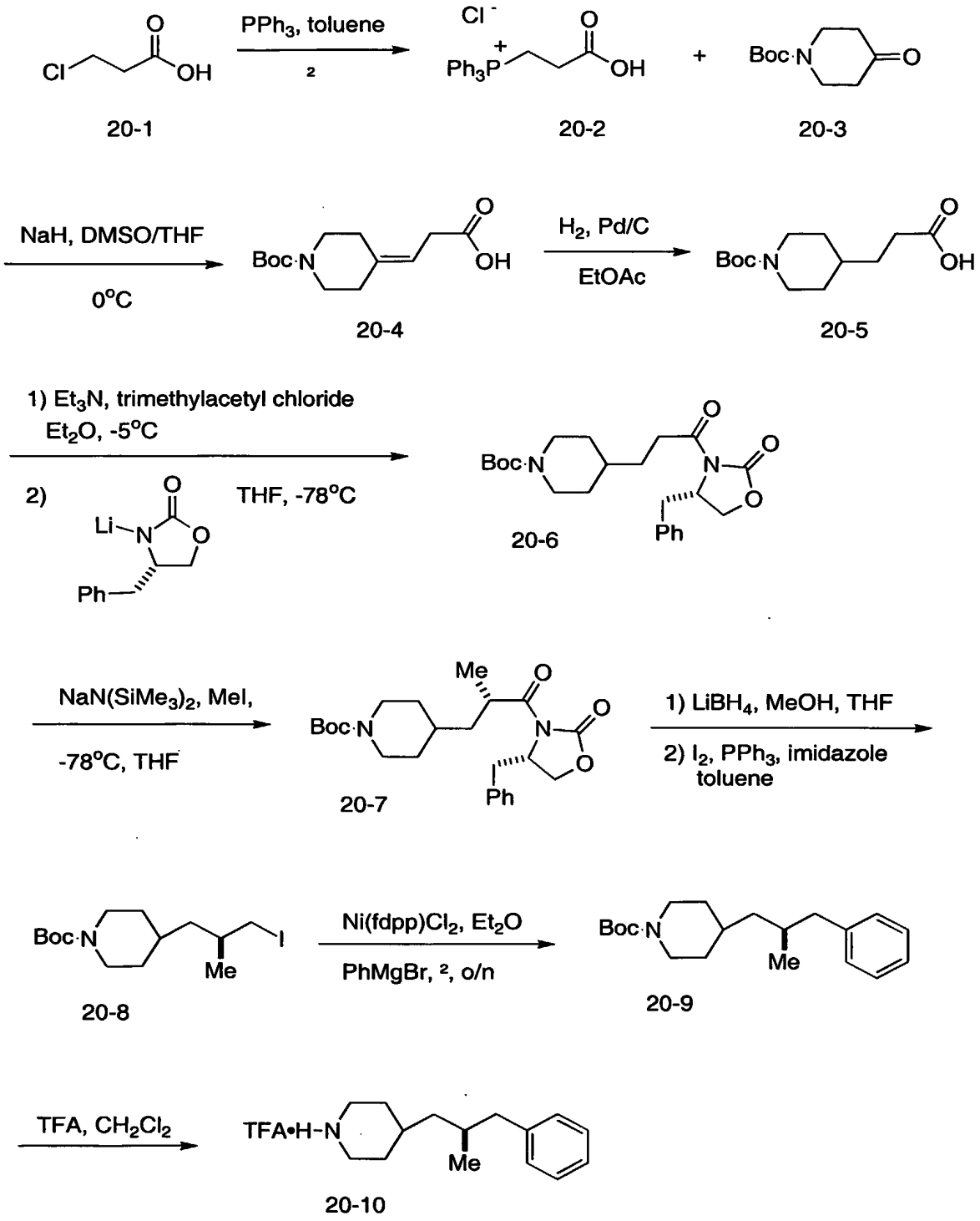
SCHEME 19



A route for the preparation of 4-(3-arylpropyl)piperidines is given in Scheme 19. Treatment of phosphonoacetate 19-1 with KHMDS followed by addition of commercially available N-Boc -4-piperidone 19-2 provides unsaturated ester 19-3. Hydrogenation of 19-3 followed by hydrolysis to the acid and then reduction with borane•methyl sulfide then affords primary alcohol 19-4. Mild oxidation of 19-4 under Swern conditions provides the corresponding aldehyde, which upon treatment with the Wittig reagent prepared from methyltriphenylphosphonium iodide and KHMDS yields olefin 19-5. Palladium-catalyzed arylation of 19-5 then affords unsaturated derivative 19-6. Addition of dibromocarbene (generated *in situ* from bromoform and potassium hydroxide) provides cyclopropyl derivative 19-7. Debromination is carried out by slow addition of tributyltin hydride in the presence of the radical initiator AIBN. Removal of the nitrogen protecting group under acidic

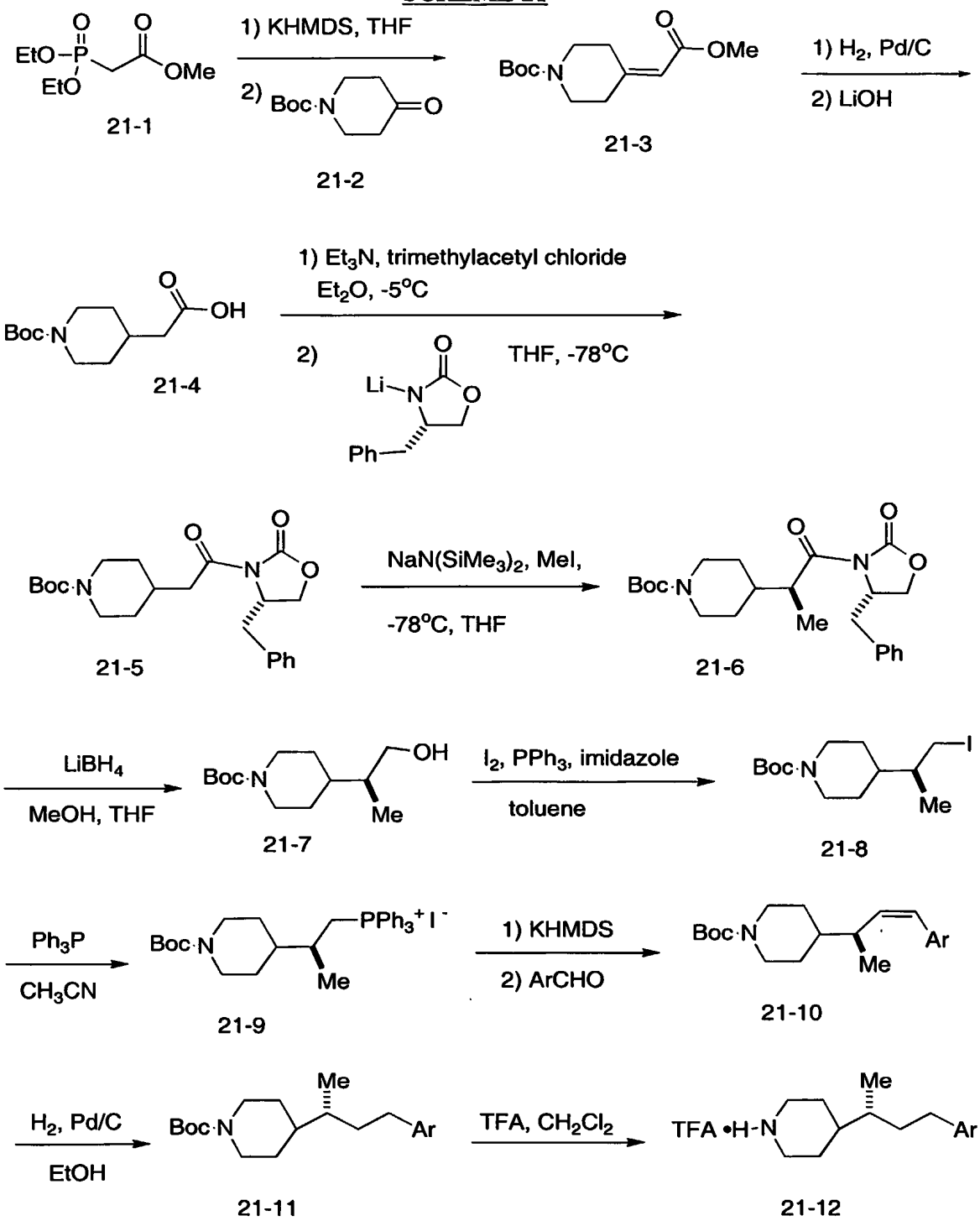
conditions, for example, hydrochloric acid in methanol, affords cyclopropyl piperidine 19-8, which can then be employed as the secondary amine component in the syntheses described above in Schemes 4, 5, 6, 7, 8, 9, 10 and 11.

SCHEME 20


PPh3, toluene
2
20-1
20-2
20-3
NaH, DMSO/THF
0°C
20-4
H2, Pd/C
EtOAc
20-5
1) Et3N, trimethylacetyl chloride
Et2O, -5°C
2)
THF, -78°C
20-6
NaN(SiMe3)2, MeI,
-78°C, THF
20-7
1) LiBH4, MeOH, THF
2) I2, PPh3, imidazole
toluene
Ni(fdpp)Cl2, Et2O
PhMgBr, 2, o/n
20-8
20-9
TFA, CH2Cl2
TFA•H-N
20-10

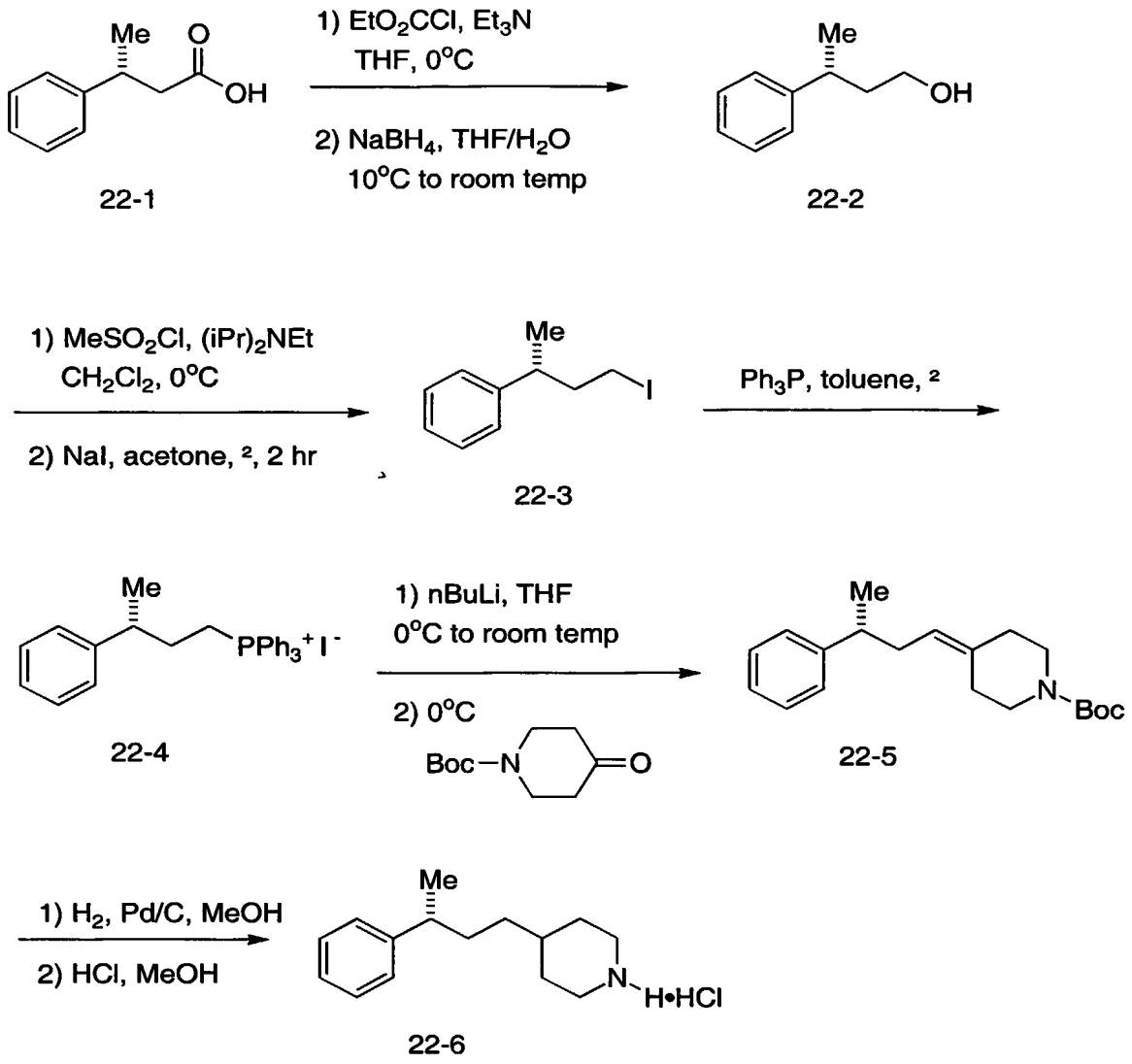
A route for the preparation of 4-(3-aryl-2-methylpropyl)piperidines is given in Scheme 20. Treatment of commercially available 3-chloropropionic acid (20-1) with triphenylphosphine in refluxing toluene provides phosphonium salt 20-2. Treatment with sodium hydride in DMSO/THF provides the ylide in situ, which upon addition of piperidone 20-3 affords the adduct 20-4. Reduction of the double bond, for example with hydrogen gas in the presence of a palladium catalyst, gives acid 20-5. Treatment of 20-5 with trimethylacetyl chloride and triethylamine generates the mixed anhydride in situ, which upon treatment with the lithium salt of 4-(S)-benzyl-2-oxazolidone yields 20-6. Deprotonation of 20-6 with sodium hexamethyldisilazide, followed by addition of methyl iodide, provides alpha-methyl derivative 20-7. Reduction of acyl-oxazolidone 20-7 with lithium borohydride produces the corresponding primary alcohol, which is converted to primary iodide 20-8 with iodine, triphenylphosphine and imidazole in toluene. Coupling with phenyl magnesium bromide in the presence of $Ni(fdpp)Cl_2$ affords aralkyl derivative 20-9, which is then deprotected under acidic conditions to provide piperidine 20-10. Piperidine 20-10 can then be employed as the secondary amine component in the syntheses described above in Schemes 4, 5, 6, 7, 8, 9, 10 and 11.

SCHEME 21


1) KHMDS, THF
2)
21-1
21-2
21-3
1) H_2, Pd/C
2) LiOH
1) Et_3N, trimethylacetyl chloride
Et_2O, -5°C
2)
THF, -78°C
21-4
NaN(SiMe$_3$)$_2$, MeI,
-78°C, THF
21-5
21-6
$LiBH_4$
MeOH, THF
21-7
I_2, PPh_3, imidazole
toluene
21-8
Ph_3P
CH_3CN
21-9
1) KHMDS
2) ArCHO
21-10
H_2, Pd/C
EtOH
21-11
TFA, CH_2Cl_2
21-12

A route for the preparation of 4-(3-aryl-1-methylpropyl)piperidines is given in Scheme 21. Addition of the anion of phosphonoester 21-1 to piperidone 21-2 provides unsaturated ester 21-3. Reduction of the double bond and hydrolysis of the ester affords acid 21-4. Treatment of 21-4 with triethylamine and trimethylacetyl chloride provides the mixed anhydride in situ, which is then coupled with the lithium salt of 4-(S)-benzyl-2-oxazolidone , to yield acyl oxazolidone 21-5. Deprotonation with sodium hexamethyldisilazide followed by addition of methyl iodide provides 21-6. Reduction of 21-6 with lithium borohydride affords alcohol 21-7, which upon treatment with iodine, triphenylphosphine and imidazole in toluene is converted to iodide 21-8. Treatment with triphenylphosphine gives phosphonium salt 21-9, which is converted to the ylide with potassium hexamethyldisilazide. Addition of an aryl aldehyde generates unsaturated aryl derivative 21-10. Hydrogenation provides saturated piperidine 21-11, which is then deprotected under acidic conditions to afford 21-12, which can then be employed as the secondary amine component in the syntheses described above in Schemes 4, 5, 6, 7, 8, 9, 10 and 11.

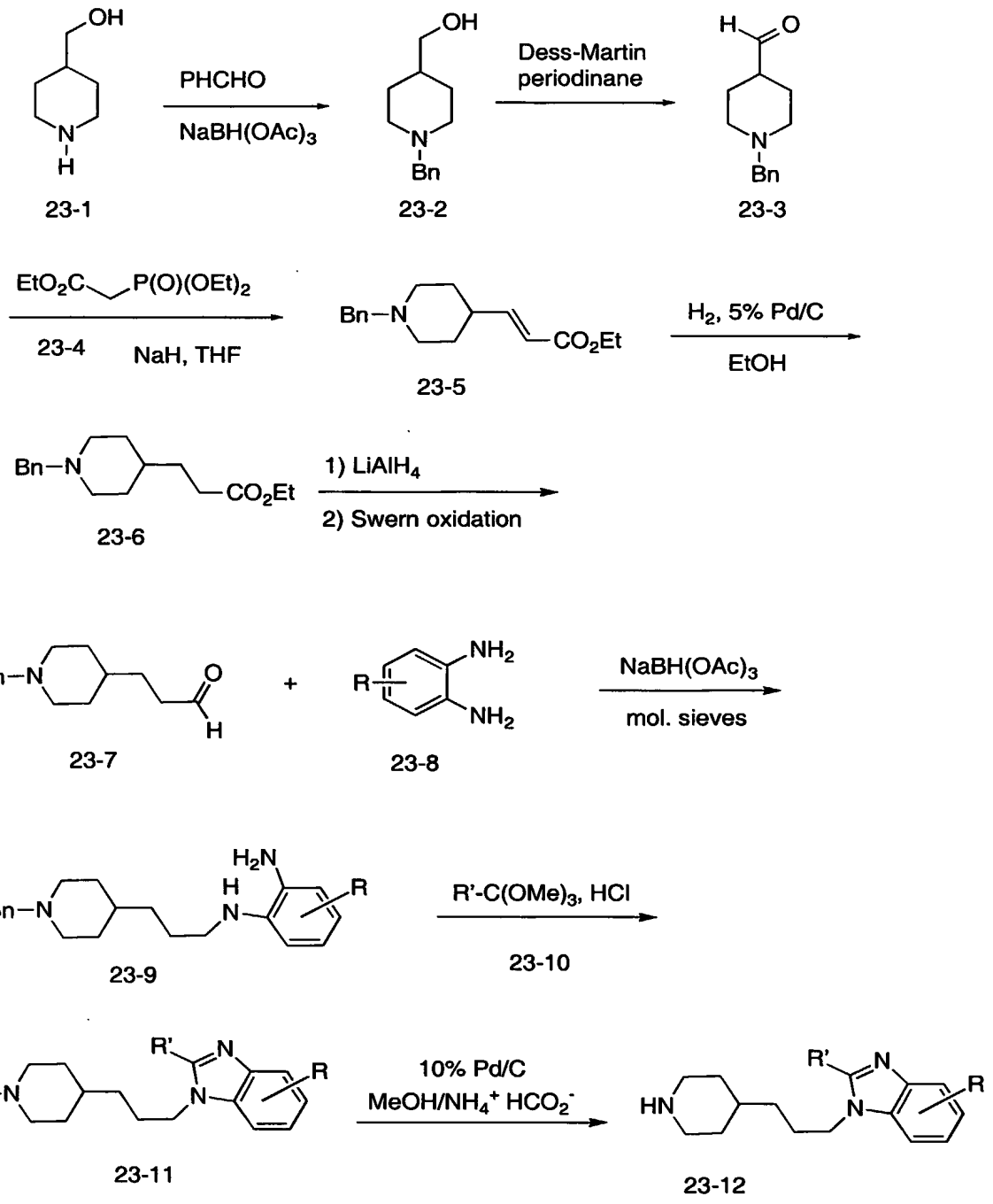
SCHEME 22



A route for the preparation of 4-(3-aryl-3-methylpropyl)piperidines is given in Scheme 22. Treatment of commercially available 4-(R)-phenylbutyric acid (22-1) with ethyl chloroformate and triethylamine forms the asymmetric anhydride in situ, which upon treatment with sodium borohydride provides primary alcohol 22-1. Alternatively, this conversion can be carried out by treatment of 22-1 with borane-THF. Activation of the hydroxy group of 22-2 with methanesulfonyl chloride in the presence of a hindered base such as N,N-(diisopropyl)ethylamine, followed by displacement with sodium iodide in refluxing acetone affords iodide 22-3. Heating with triphenylphosphine in toluene provides the phosphonium salt 22-4.

Deprotonation of this salt with a strong base, for example n-butyl lithium generates the Wittig reagent in situ, which is then allowed to react with N-Boc-4-piperidone, to yield olefin 22-5. Hydrogenation of the double bond followed by treatment with acid, for example HCl in methanol, then provides the secondary amine salt 22-6, which can then be employed as the secondary amine component in the syntheses described above in Schemes 4, 5, 6, 7, 8, 9, 10 and 11.

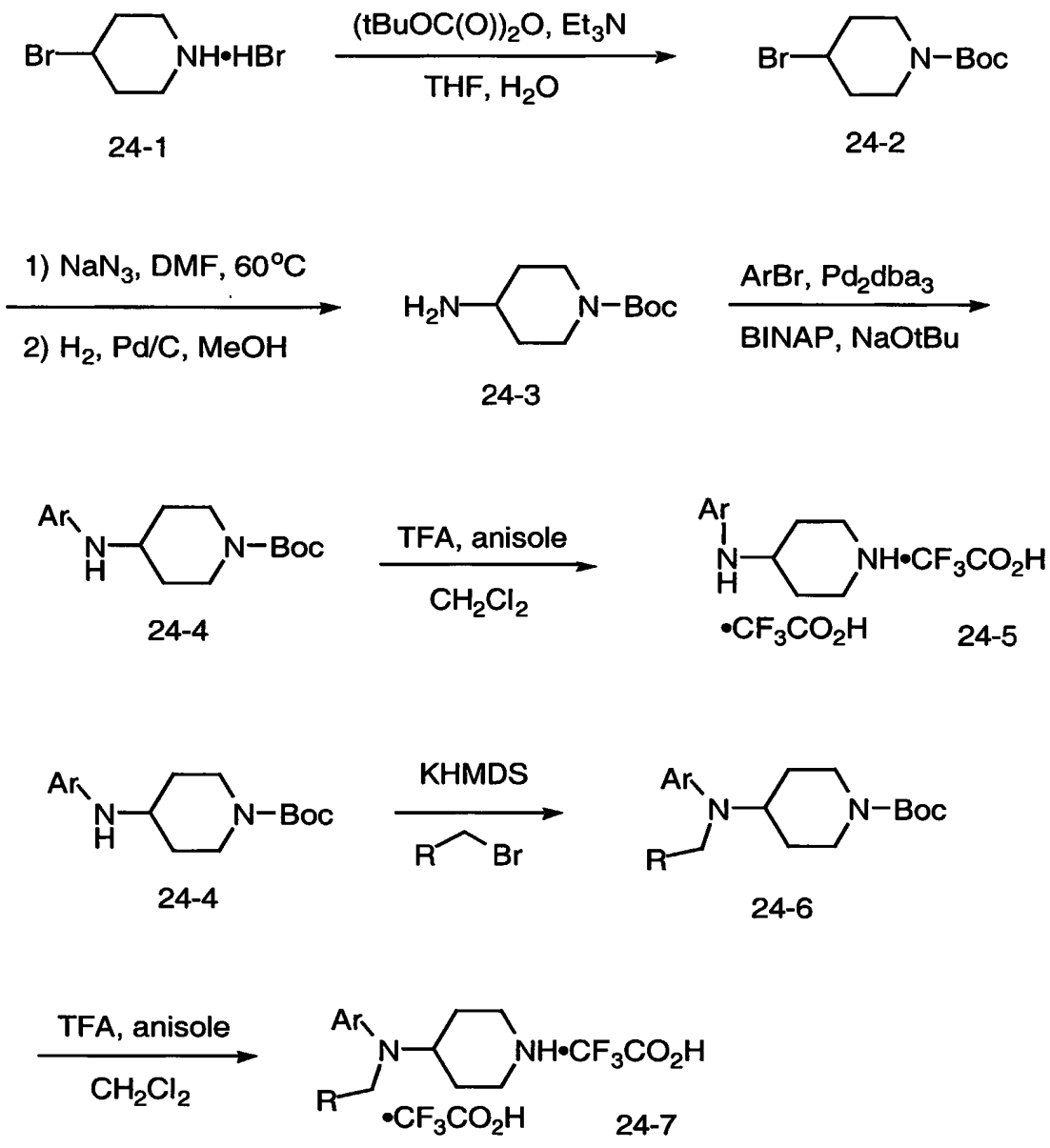
SCHEME 23



A route for the preparation of 4-(3-(benzimidazol-2-yl)propyl)piperidines is given in Scheme 23. Protection of piperidine 23-1 under reductive amination conditions provides benzylamine 23-2. Oxidation to aldehyde

23-3 is carried out under standard conditions, for example with the Dess-Martin periodinane. Addition of ester 23-4 provides unsaturated olefin 23-5, which upon reduction affords ester 23-6. Reduction with lithium aluminum hydride or other strong hydride reducing agents followed by mild oxidation provides aldehyde 23-7. Upon combination with diamine 23-8 under reductive alkylation conditions affords the N-alkylated derivative 23-9. Treatment with orthoformate derivative 23-10 in the presence of acid yields benzimidazole 23-11, which upon hydrogenation with palladium on carbon under transfer hydrogenation conditions generates piperidine 23-12, which can then be employed as the secondary amine component in the syntheses described above in Schemes 4, 5, 6, 7, 8, 9, 10 and 11.

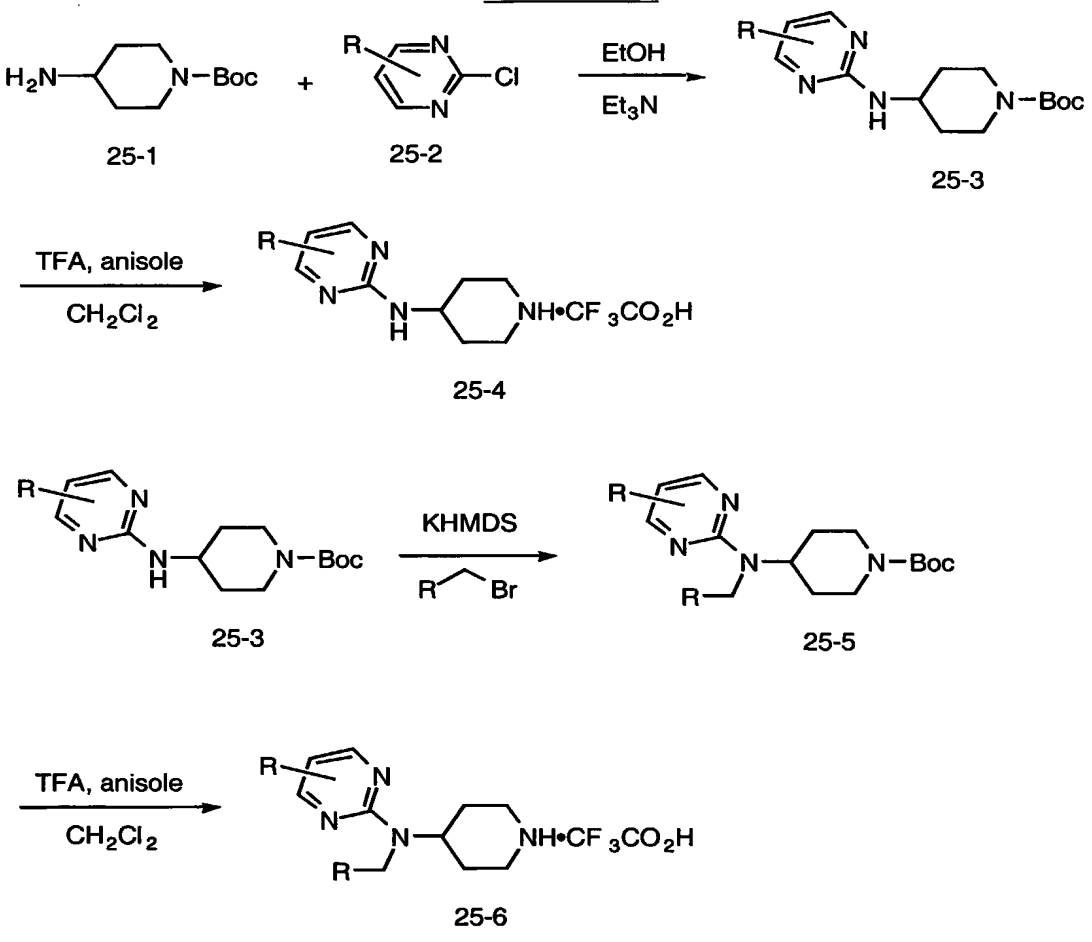
SCHEME 24



Procedures for synthesizing certain CCR5 receptor modulators containing 4-(heteroarylamino)piperidine functionality are shown in Scheme 24. After protecting commercially available 4-bromopiperidine, the bromide is displaced with sodium azide, and the azide is reduced, for example by catalytic reduction, to provide aminopiperidine 24-3. Treatment of 24-3 with an aryl or heteroaryl halide (the halide preferably being bromide) in the presence of a palladium catalyst, sodium t-butoxide and a suitable bidentate ligand (such as BINAP), according to the

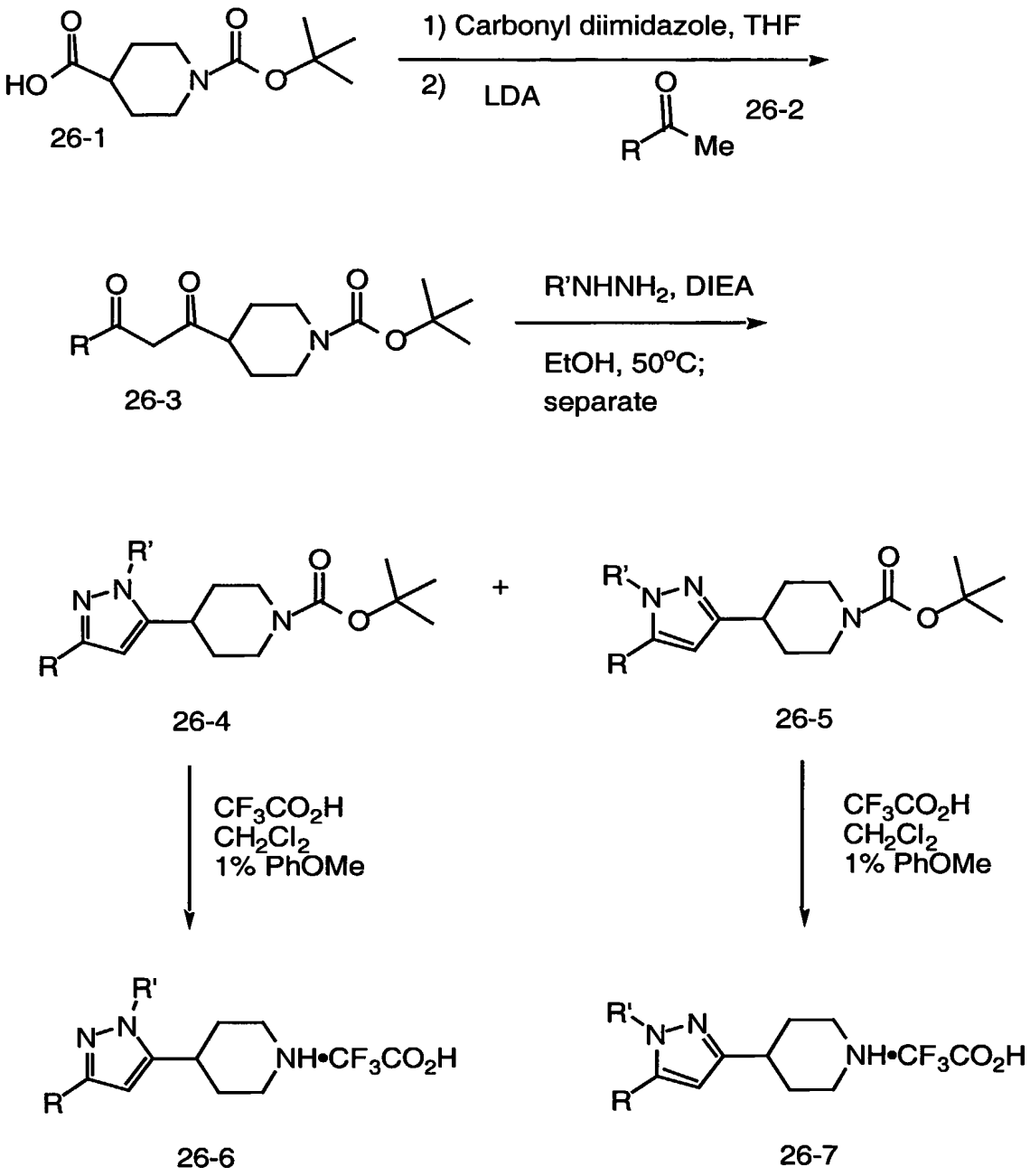
conditions of Buchwald et al (**REF**), provides arylamine 24-4. Direct acidic deprotection of 24-4 may be carried out to provide secondary amine 24-5. Alternatively, amine 24-4 may be alkylated with a suitable alkyl, alkenyl or alkynyl halide (wherein the halide is bromo or iodo in the case of an alkyl group and chloro or bromo in the case of allylic or propargylic functionality) in the presence of a strong base, such as potassium hexamethyldisilazide, to provide trisubstituted amine 24-6. Acidic deprotection, for example, trifluoroacetic acid and anisole in dichloromethane, or methanolic hydrochloric acid, then provides the bis ammonium salt, which in the case of trifluoroacetic acid deprotection, is compound 24-7. The secondary piperidines 24-5 and 24-7 are then utilized as the cyclic secondary amine component as shown above in Schemes 4, 5, 6, 7, 8, 9, 10 and 11.

SCHEME 25



For certain aminoheterocycles, direct displacement of a halogen may provide improved access to the desired intermediates. For example, as shown in Scheme 25, unsubstituted and substituted 2-chloropyrimidines 25-2 may be coupled directly to amine 25-1 in the presence of a suitable base, such as triethylamine, to provide aminopyrimidine 25-3. Acidic deprotection then affords 25-4. Alternatively, 25-3 may be alkylated in the presence of a strong base to provide 25-5, which upon deprotection gives intermediate 25-6. The secondary piperidines 25-4 and 25-6 are then utilized as the cyclic secondary amine component as shown in Schemes 4, 5, 6, 7, 8, 9, 10 and 11.

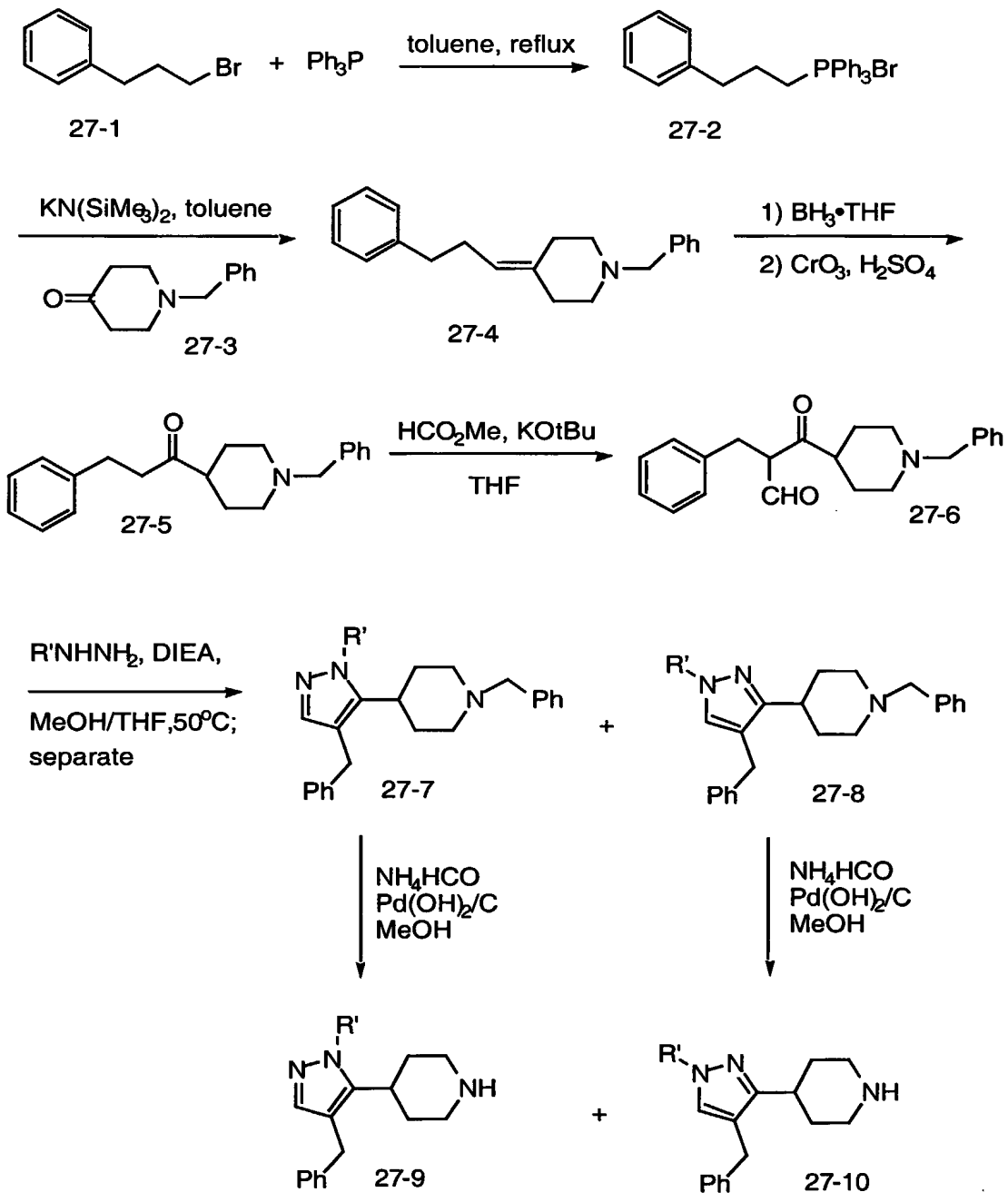
SCHEME 26



One preparation of piperidine subunits containing functionalized pyrazoles at C-4 of the piperidine is given in Scheme 26. Treatment of piperidine 26-1 with carbonyldiimidazole to form the acyl imidazole, followed by addition of a dialkyl or alkyl-aryl ketone (26-2) in the presence of lithium diisopropylamide (LDA) gives the diketone 26-3. Treatment with a monoalkyhydrazine in an alcohol solvent

at temperatures between 0 to 100 degrees C (preferably about 50 degrees C) in the presence of a hindered base such as DIPEA then provides a mixture of the isomeric pyrazoles 26-4 and 26-5. After separation of these compounds by chromatography or crystallization, the individual products are deblocked under acidic conditions (for example trifluoroacetic acid and anisole with or without methylene chloride as a co-solvent) to provide the piperidine salts 26-6 and 26-7, which are then used as the cyclic secondary amine component as shown above in Scheme 2 and in Schemes 4, 5, 6, 7, 8, 9, 10 and 11.

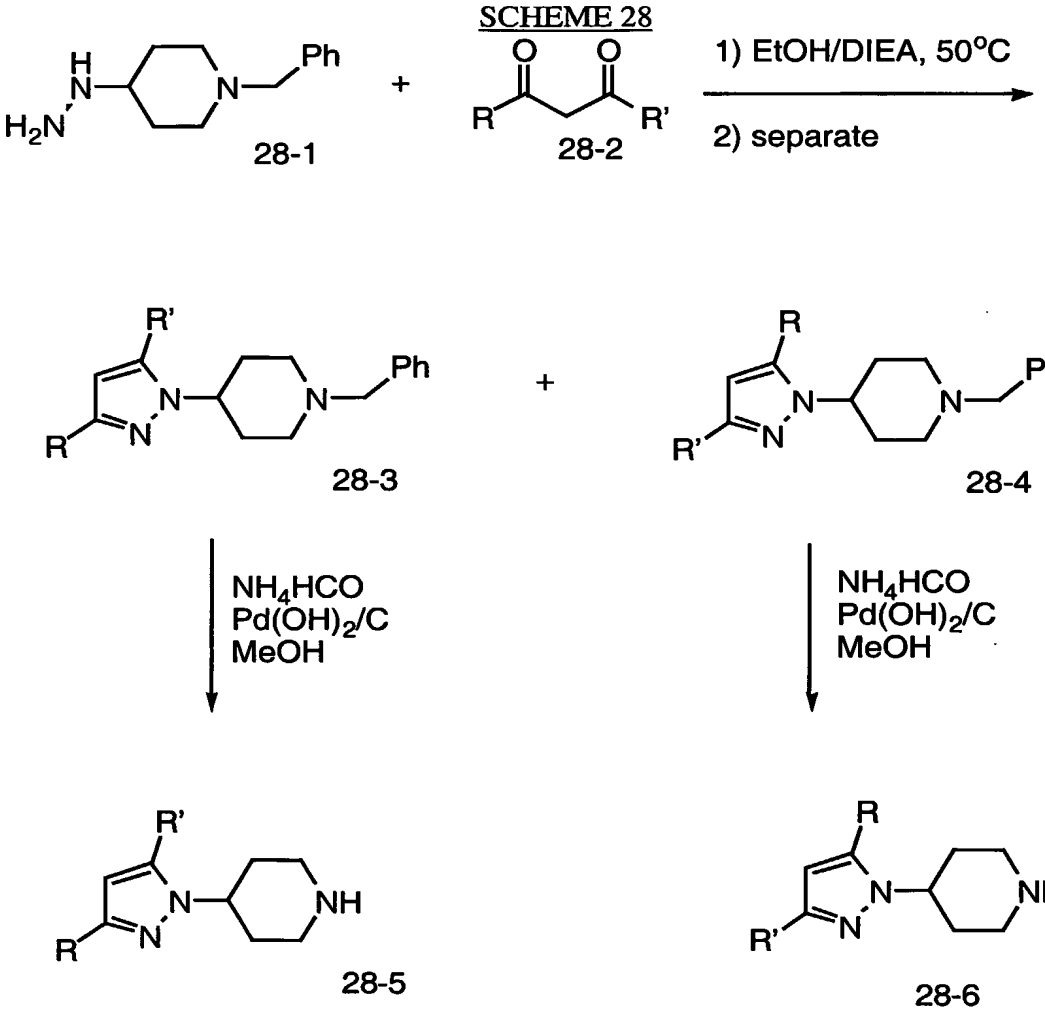
SCHEME 27



Another preparation of piperidine subunits containing functionalized pyrazoles at C4 of the piperidine is given in Scheme 27. Treatment of commercially available bromide 27-1 with triphenylphosphine in refluxing toluene provides phosphonium salt 27-2, which after treatment with a strong anhydrous base such as

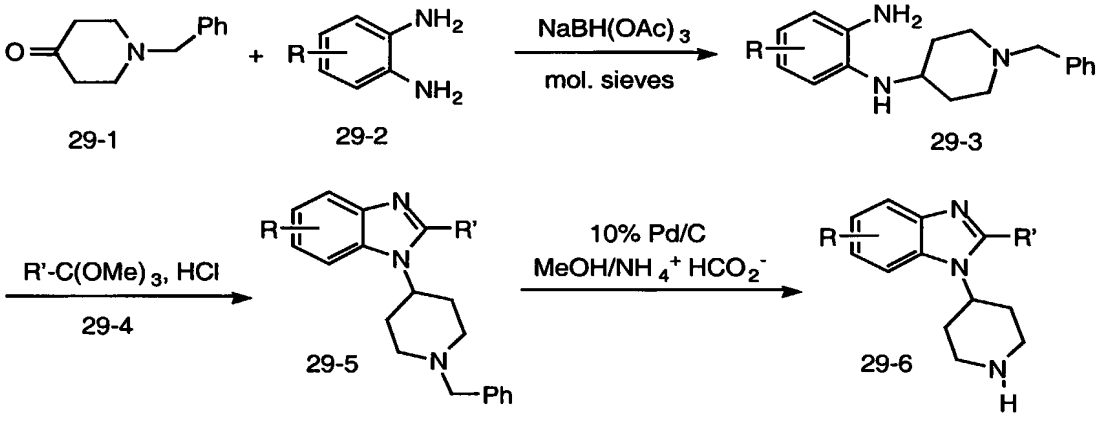
potassium hexamethyldisilazide in toluene and the piperidine ketone 27-3 provides the olefin 27-4. Hydroboration followed by an oxidative work-up with chromic acid then affords ketone 27-5. Selective formylation of 27-5 with methyl formate in the presence of potassium t-butoxide selectively affords ketoaldehyde 27-6. Heating of 27-6 with a monoalkylhydrazine in methanol in the presence of a hindered (or insoluble) base such as DIPEA then provides a mixture of the 1,4-disubstituted pyrazoles 27-7 and 27-8. After separation by chromatography, crystallization or fractional distillation, the purified isomers are deprotected under transfer hydrogenation conditions to provide the piperidines 27-9 and 27-10, which are then utilized as the cyclic secondary amine component as shown above in Schemes 4, 5, 6, 7, 8, 9, 10 and 11.

SCHEME 28



A preparation of piperidine subunits containing 3,5-difunctionalized pyrazoles linked through N-1 to C-4 of the piperidine is given in Scheme 28. Treatment of commercially available hydrazine 28-1 with diketone 28-2 in ethanol at 0 to 90 degrees C (preferably 50 degrees C) in the presence of DIPEA provides a mixture of pyrazoles 28-3 and 28-4, which are separated under standard conditions, for example HPLC. Removal of the benzyl groups by transfer hydrogenation provides the secondary piperidines 28-5 and 28-6, which are then utilized as the cyclic secondary amine component as shown above in Schemes 4, 5, 6, 7, 8, 9, 10 and 11.

SCHEME 29



A preparation of 4-(benzimidazol-1-yl)piperidine subunits is given in Scheme 29. Combining piperidone 29-1 and diamine 29-2 in the presence of sodium triacetoxyborohydride under dehydrating conditions provides reductive amination product 29-3. Addition of a suitably substituted ortho ester 29-4 in the presence of a acid catalyst, for example concentrated hydrochloric acid, provides benzimidazole intermediate 29-5. Deprotection under reductive conditions, for example with palladium on carbon under transfer hydrogenation conditions, then provides secondary amine 29-6, which is then utilized as the cyclic secondary amine component as shown above in Schemes 4, 5, 6, 7, 8, 9, 10 and 11.

In some cases the order of carrying out the foregoing reaction schemes may be varied to facilitate the reaction or to avoid unwanted reaction products. The

following examples are provided for the purpose of further illustration only and are not intended to be limitations on the disclosed invention.

GENERAL

Concentration of solutions was carried out on a rotary evaporator under reduced pressure. Flash chromatography was carried out on silica gel (230-400 mesh). NMR spectra were obtained in $CDCl_3$ solution unless otherwise noted. Coupling constants (J) are in hertz (Hz). Abbreviations: diethyl ether (ether), triethylamine (TEA), N,N-diisopropylethylamine (DIEA) saturated aqueous (sat'd), room temperature (rt), hour(s) (h), minute(s) (min).

HPLC CONDITIONS

HPLC A. Retention time using the following conditions: Column: YMC ODS A, 5 μ, 4.6 x 50 mm; Gradient Eluent: 10:90 to 90:10 v/v acetonitrile/water + 0.5% TFA over 4.5 min, hold 30 sec; Detection: PDA, 210-400 nm; Flow Rate: 2.5 mL/min.

HPLC B. Retention time using the following conditions: Column: Analytical Sales & Services Advantage HL C18 5 μ 4.6 x 100 mm column; Gradient Eluent: 10:90 to 90:10 v/v acetonitrile /water + 0.5% TFA over 10 min, hold 2 min; Detection: PDA, 200-400 nm; Flow Rate: 2.25 mL/min.

The following are representative Procedures for the preparation of the piperidines used in the following Examples or which can be substituted for the piperidines used in the following Examples and which are not commercially available.

PROCEDURE 1

4-(3-Benzyl-1-ethyl-(1H)-pyrazol-5-yl)piperidine di-trifluoroacetic acid salt

Step A: 1-(1-(t-Butoxycarbonyl)piperidin-4-yl)-4-phenylbutane-1,3-dione Method A:

n-Butyl lithium (100 mL, 0.16 mole) was added to a stirred solution of diisopropylamine (16.16 g, 22.4 mL, 0.16 mole, distilled) in THF (450 mL) at 0 °C

over 45 min under nitrogen. Stirring was continued for 10 min at 0 °C after the addition was complete. After cooling to -78 °C, phenylacetone (21.45 g, 21.13 mL, 0.16 mole) in THF (100 mL) was added dropwise over 15 min with stirring. This solution was stirred at -78 °C for 1 h. Meanwhile, a solution of *N*-Boc isonipecotic acid (18.32 g, 0.080 mole) and carbonyl diimidazole (12.98 g, 0.080 mole) in THF (150 mL) was prepared. After stirring for 15 min, this solution was canulated into the enolate solution dropwise over 15 min. The reaction was stirred at <-70 °C for 1 h and then allowed to warm to rt over 3 h. The reaction was quenched with 1M citric acid (250 mL) and stirred for 16 h. The organic layer was separated and washed with 250 mL each of saturated sodium bicarbonate solution, water and brine. After drying over sodium sulfate, the organic layer was concentrated to give an oil. The residue was purified by FC on silica gel (10% ethyl acetate in 60-80 °C petroleum ether) to give separation of the two isomers. The first higher R_f fractions afforded pure title compound as the minor product (3.5 g) as an oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34-7.37 (m, 2 H), 7.25-7.31 (m, 3 H), 5.46 (s, 1 H), 4.11-4.17 (m, 2 H), 3.63 (s, 2 H), 2.70-2.76 (m, 2 H), 2.29 (tt, J = 11.7 and 3.7 Hz, 1 H), 1.75-1.80 (m, 2 H), 1.47-1.61 (m, 2 H), 1.47 (s, 9 H).

MS (ESI): m/z 346 (M + 1).

The lower R_f fractions contained phenylacetone and major product 1-(1-(t-butoxycarbonyl)piperidin-4-yl)-2-phenylbutane-1,3-dione from which the latter crystallized on standing to give 7 g white solid (m.p. 105-106 °C).

^{1}H NMR (360 MHz, $CDCl_3$): δ 15.23 (s, 1 H), 7.3-7.45 (m, 3 H), 7.15-7.2 (m, 2 H), 4-4.1 (m, 2 H), 2.35-2.50 (m, 2 H), 2.2-2.3 (m, 1 H), 1.87 (s, 3 H), 1.5-1.75 (m, 4 H), 1.43 (s, 9 H).

MS (ESI): m/z 346 (M + 1).

Method B:

Step B1: 1-(t-Butoxycarbonyl)piperidine-4-*N*-methyl-*N*-methoxycarboxamide

N-Boc isonipecotic acid (13.56 g, 59.2 mmol), N,O-dimethyl hydroxylamine hydrochloride (8.65 g, 88.7 mmol), and 1-hydroxybenzotriazole hydrate (15.9 g, 118 mmol) were dissolved in DMF (225 mL) in a 500 mL round-bottom flask and diisopropylethylamine (15.3 g, 20.6 mL, 118.3 mmol) was then added with stirring at rt. 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (17.01 g, 88.74 mmol) was added in several portions over 10 min with stirring. After 22 h, the

reaction mixture was poured into a water and ice mixture (600 mL) and was extracted with ethyl acetate (5 x 125 mL). The combined organic layers were washed with 1N HCl (2 x 200 mL), 5% sodium bicarbonate (2 x 200 mL), water and brine, dried over sodium sulfate and concentrated to give the title compound (15.58 g) as a yellowish oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.11-4.20 (m, 2 H), 3.72 (br s, 3 H), 3.20 (br s, 3 H), 2.75-2.86 (m, 3 H), 1.63-1.76 (m, 4 H), 1.47 (s, 9 H).

Step B2: 4-Acetyl-1-(t-butoxycarbonyl)piperidine

After dissolving the Weinreb amide from Step B1 in anhydrous ether (400 mL) under nitrogen and cooling the solution in an ice bath, 1.4M methyl magnesium bromide (55 mL) in 3:1 toluene and THF was added with stirring and cooling over 30 min. After stirring at 0 °C for 1 h, the reaction was poured into a mixture of ice water (400 mL) and acetic acid (8 mL, 150 mmol). The layers were separated and the aqueous layer was extracted twice with ether. The combined organic layers were washed with 0.1N HCl (200 mL), 3% sodium bicarbonate (200 mL), water (200 mL) and brine (200 mL), dried over sodium sulfate, and concentrated to give the crude product (14.322 g). FC (20-80% ethyl acetate in hexanes) gave the title compound (9.440 g) as a yellowish oil. R_f: 0.27 (25% ethyl acetate in hexanes). Some starting Weinreb amide was also recovered (3.212 g). R_f: 0.10 (25% ethyl acetate in hexanes).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.07-4.14 (m, 2 H), 2.75-2.83 (m, 2 H), 2.46 (tt, J = 11.3 and 3.8 Hz, 1 H), 2.17 (s, 3 H), 1.82-1.87 (m, 2 H), 1.48-1.57 (m, 2 H), 1.46 (s, 9 H).

Step B3: 1-(1-(t-Butoxycarbonyl)piperidin-4-yl)-4-phenylbutane-1,3-dione

To a suspension of 60% sodium hydride (1.07 g) in THF (15 mL) at 0°C was added a solution of 4-acetyl-1-(t-butoxycarbonyl)piperidine from Step B2 (3.03 g, 13.3 mmol) and methyl phenylacetate (6.01 g, 39.9 mmol) in THF (6 mL) over 20 min. The reaction was stirred for another 4 h as it was allowed to warm to rt. The mixture was diluted with ether (30 mL) and poured into 1N HCl. The layers were separated and the aqueous layer was extracted three times with ether. The combined organic layers were washed with brine (150 mL), dried over sodium sulfate and concentrated. The crude product was purified by FC (20% ethyl acetate in hexanes) to

give the title compound (3.02 g). R_f: 0.30 (20% ethyl acetate in hexane). The ^1H NMR data was the same as that obtained from the product of Method A.

Step B: 4-(5-Benzyl-1-ethyl-(1H)-pyrazol-3-yl)-1-(t-butoxycarbonyl)piperidine (Higher R_f isomer) and 4-(3-benzyl-1-ethyl-(1H)-pyrazol-5-yl)-1-(t-butoxycarbonyl)piperidine (Lower R_f isomer)

Method A:

1-(1-(t-Butoxycarbonyl)piperidin-4-yl)-4-phenylbutane-1,3-dione from Step A, from Method A or Method B, Step B3, (0.851 g, 2.46 mmol) in methanol (25 mL) was added over 10 min to a suspension of ethylhydrazine oxalate (0.444 g, 2.96 mmol) in methanol (5 mL) in a 60 °C oil bath. After 15 h, the reaction was concentrated *in vacuo* and the residue was purified by repeated FC using a gradient of 50-100% ethyl acetate in hexanes to give first 4-(5-benzyl-1-ethyl-(1H)-pyrazol-3-yl)-1-(t-butoxycarbonyl)piperidine (0.148 g total) as the higher R_f product isomer and then the title compound (0.373 g total) as the lower R_f.

Higher R_f isomer:

^1H NMR (500 MHz, $CDCl_3$): δ 7.2-7.3 (m, 2 H), 7.3-7.4 (m, 1 H), 7.17 (d, J = 7.5 Hz, 2 H), 5.77 (s, 1 H), 4.0-4.25 (m, 2 H), 3.97 (q, J = 7.3 Hz, 2 H), 3.95 (s, 2 H), 2.7-2.9 (m, 2 H), 2.76 (tt, J = 11.3 and 3.8 Hz, 1 H), 1.92 (br d, J = 13 Hz, 1 H), 1.5-1.65 (m, 2 H), 1.47 (s, 9 H), 1.29 (t, J = 7.3 Hz, 3 H).

Lower R_f isomer:

^1H NMR (500 MHz, $CDCl_3$): δ 7.25-7.4 (m, 3 H), 7.2 (m, 2 H), 5.72 (s, 1 H), 4.1-4.3 (m, 2 H), 4.08 (q, J = 7.1 Hz, 2 H), 3.95 (s, 2 H), 2.7-2.9 (m, 2 H), 2.66 (tt, J = 11.3 and 3.8 Hz, 1 H), 1.82 (br d, J = 12.8 Hz, 1 H), 1.4-1.6 (m, 2 H), 1.48 (s, 9 H), 1.47 (t, J = 7.1 Hz, 3 H).

Method B:

Step B1: 1-(t-Butoxycarbonyl)-4-hydroxymethylpiperidine

A solution of 25.03 g (109.2 mmole) N-Boc isonipecotic acid was dissolved in 200 mL THF and treated with 200 mL 1 M borane-tetrahydrofuran complex in THF, and the mixture was stirred overnight. The mixture was concentrated under vacuum, diluted with 750 mL ethyl acetate, and washed with 150 mL 1 N HCl (6x) and then saturated brine. The organic layer was dried over sodium

sulfate and concentrated to give 24.3 g of crude product as a white solid. This was used as is in the next step.

^{1}H NMR (500 MHz) δ 4.15 (br d, J=13.7 Hz, 2H), 3.52 (d, J=6.2 Hz, 2H), 2.69~2.75 (m, 2H), 1.71~1.75 (m, 2H), 1.62~1.70 (m, 1H), 1.47 (s, 9H), 1.12~1.21 (m, 2H).

Step B2: 1-(t-Butoxycarbonyl)-4-formylpiperidine

A mixture of 17.62 g (135.6 mmole) oxalyl chloride and 250 mL methylene chloride in a dry ice acetone bath. was treated with a solution of 21.19 g (271.2 mmole) DMSO in 150 mL methylene chloride over 20 minutes. After stirring for 20 minutes, a solution of 24.327 g 1-(t-butoxycarbonyl)-4-hydroxymethylpiperidine (from Step B1 above) in 150 mL methylene chloride was added over 1 h. After an additional 15 minutes, 57.17 (565 mmole) triethylamine in 150 mL methylene chloride was added over half an hour. The reaction mixture was allowed to warm up over night in the cooling bath. The reaction mixture was concentrated under vacuum to remove about 400 mL methylene chloride, and the residue was partitioned between 1 L ether and 300 mL water. To this was added 200 mL 1 N NaOH, the layers were separated, and the organic layer was washed with 150 mL 1 N NaOH (2x), water (3x), and saturated brine, dried over sodium sulfate, and concentrated to give 22.562 g crude product. FC (10~60% ethyl acetate in hexanes) gave 20.58 g title compound as slightly yellowish oil.

R_F: 0.29 (3:1 v/v hexanes/ethyl acetate).

^{1}H NMR (500 MHz) δ 9.68 (d, J=0.7 Hz, 1H), 3.96~4.02 (m, 2H), 2.92~2.97 (m, 2H), 2.40~2.45 (m, 1H), 1.88~1.94 (m, 2H), 1.53~1.64 (m, 2H), 1.47 (s, 9H).

Step B3: 1-(t-Butoxycarbonyl)-4-(2,2-dibromoethen-1-yl)piperidine

A solution of 48.615 g (146.6 mmole) carbon tetrabromide in 150 mL methylene chloride was added dropwise with stirring to a solution of 76.895 g (293.2 mmole) triphenylphosphine in 150 mL methylene chloride in a 1-L rb flask with ice bath cooling over 1.75 h. After 40 minutes, a solution of 15.631 g (73.29 mmole) 1-(t-butoxycarbonyl)-4-formylpiperidine (from Step B2 above) in 100 mL methylene chloride was added to the resulting brown suspension with stirring and cooling over 40 minutes. After one hour, 200 mL ether and 400 mL hexanes was added. The top suspension was filtered through Celite, and the residue was resuspended in 150 mL methylene chloride and treated with 300 mL ether. The mixture was filtered, and the solid was washed with hexanes until the total filtrate was 2 L. The filtrate was filtered

again through Celite and washed with hexanes. The filtrate was washed with 100 mL 5% sodium bicarbonate, 300 mL water (2x), and 150 mL brine. The organic layer was dried over sodium sulfate and concentrated under vacuum to give 53.5 g crude product as a yellowish solid. Flash chromatography (FC) on 250 g silica gel (0~15% ethyl acetate in hexanes) gave 21.595 g title compound as a white solid.

R_f: 0.57 (15% ethyl acetate in hexanes).

^{1}H NMR (500 MHz) δ 6.25 (d, J=8.9 Hz, 1H), 4.04~4.12 (m, 2H), 2.75~2.83 (m, 2H), 2.42~2.50 (m, 1H), 1.69~1.75 (m, 2H), 1.47 (s, 9H), 1.29~1.37 (m, 2H).

Step B4: 1-(t-Butoxycarbonyl)-4-(2-tributylstannylethyn-1-yl)piperidine

A mixture of 23.199 g (62.85 mmole) 1-(t-butoxycarbonyl)-4-(2,2-dibromoethen-1-yl)piperidine (prepared as in Step B3 above) and 600 mL anhydrous THF was cooled with dry ice acetone bath under nitrogen. To this mixture was added 88 mL of a 1.6 M butyl lithium solution in hexanes dropwise with stirring and cooling over 50 minutes. After one hour, the flask was transferred into an ice bath. After another hour, a solution of 28.64 g (87.99 mmole) tributyltin chloride in 100 mL THF was added with stirring and cooling over 35 minutes. After three h, the mixture was concentrated under vacuum to remove some THF, and the residue was partitioned between 600 mL ice water and 800 mL ether. The organic layer was washed with 200 mL of water (1x), 2% sodium bicarbonate (1x), water (2x), and saturated brine (1x), dried over sodium sulfate and concentrated under vacuum to give 30.104 g crude product as a green-yellowish liquid. FC on 275 g silica gel using cold 2.5~15% ethyl acetate in hexanes as quickly as possible to give 27.115 g title compound as a colorless liquid.

R_f: 0.45 (10% ethyl acetate in hexanes).

^{1}H NMR (500 MHz) δ 3.63~3.67 (m, 2H), 3.25~3.30 (m, 2H), 2.64~2.69 (m, 1H), 1.74~1.79 (m, 2H), 1.54~1.64 (m, 8H), 1.47 (s, 9H), 1.32~1.39 (m, 6H), 0.96~0.99 (m, 6H), 0.92 (t, J=7.3 Hz, 9H).

Step B5: 4-(1-(t-Butoxycarbonyl)piperidin-4-yl)-1-phenylbutan-2-on-3-yne

To a mixture of 1.727 g (3.466 mmole) 1-(t-butoxycarbonyl)-4-(2-tributyl-stannylethyn-1-yl)piperidine (prepared in Step B4 above) in 18 mL 1,2-dichloroethane was added 0.536 g (3.466 mmole) phenylacetyl chloride and 50 mg dichlorobis-(triphenylphosphine)palladium (II). The mixture was refluxed under

nitrogen for 2 h, then concentrated under vacuum. Purification of the residue on silica gel (5~35% ethyl acetate in hexanes) gave 0.784 g title compound as a yellow oil. R_f: 0.27 (20% ethyl acetate in hexanes).

^{1}H NMR (500 MHz) δ 7.34~7.38 (m, 2H), 7.28~7.32 (m, 1H), 7.24~7.27 (m, 2H), 3.82 (s, 2H), 3.49~3.54 (m, 2H), 3.17~ 3.23 (m, 2H), 2.68~2.73 (m, 1H), 1.72~1.77 (m, 2H), 1.51~1.57 (m, 2H), 1.47 (s, 9H).

Tetrakis(triphenylphosphine)palladium gave a similar result.

Step B6: 4-(3-Benzyl-1-ethyl-(1H)-pyrazol-5-yl)-1-(tert-butoxycarbonyl) piperidine

Heating 1.204 g (3.677 mmole) 4-(1-(t-butoxycarbonyl)piperidin-4-yl)-1-phenylbutan-2-on-3-yne (prepared in Step B5 above) with 0.662 g (4.413 mmole) ethylhydrazine oxalate and 1.252 g (9.687 mmole) DIEA in 20 mL ethanol over night gave an 8:1 ratio of the title compound and its isomer 4-(5-benzyl-1-ethyl-(1H)-pyrazol-3-yl)-1-(tert-butoxycarbonyl)piperidine. Use of ethylhydrazine free base gave even more favorable ratios of the desired title compound. The desired isomer can be isolated by recrystallization using hexanes or by silica gel chromatography using 5~10% acetonitrile in methylene chloride in addition to the procedure described in Method A above.

Step C: 4-(3-Benzyl-1-ethyl-(1H)-pyrazol-5-yl)piperidine di-TFA salt

To a solution of 4-(3-benzyl-1-ethyl-(1H)-pyrazol-5-yl)-1-(t-butoxycarbonyl)piperidine from Step B (lower R_f isomer) (0.373 g, 1.01 mmol) and anisole (0.219 mL, 2.02 mmol) in methylene chloride (15 mL) was added trifluoroacetic acid (1.555 mL, 20.2 mmol). The reaction was stirred at rt for 2.5 h and then concentrated. The residue was purified on preparative reverse-phase HPLC using 9.4 x 250 mm Semi-preparative Zorbax SB-C18 column with 17.5-35% acetonitrile gradient in water having 0.5% (v/v) TFA over 15 min at 6.05 mL per minute to give the title di-TFA salt compound as an oil. When a mixture of isomers from Step B is used, separation is also possible at this step with the above Prep HPLC conditions in which the title isomer elutes prior to 4-(5-benzyl-1-ethyl-(1H)-pyrazol-3-yl)piperidine.

PROCEDURE 2

4-(3-Benzyl-(1H)-pyrazol-5-yl)piperidine di-trifluoroacetic acid salt

Step A: 4-(3-Benzyl-(1H)-pyrazol-5-yl)-1-(t-butoxycarbonyl)piperidine TFA salt

A solution of 1-(1-(t-butoxycarbonyl)piperidin-4-yl)-4-phenyl-butane-1,3-dione from Procedure 1, Step A (30 mg, 0.087 mmol), hydrazine di-hydrochloride (10.9 mg, 0.1 mmol) and DIPEA (0.045 mL, 0.25 mmol) in methanol (1 mL) was heated at 50 °C for 16 h. The volatiles were then removed under reduced pressure. Purification of the residue was done on preparative reverse-phase HPLC using a 9.4 x 250 mm Semi-preparative Zorbax SB-C18 column with 35-50% acetonitrile gradient in water having 0.5% (v/v) TFA over 15 min to give the title compound (45.2 mg) as a gel.

Step B: 4-(3-Benzyl-(1H)-pyrazol-5-yl)piperidine di-TFA salt

To a solution of 4-(3-benzyl-(1H-pyrazol-5-yl))-1-(t-butoxycarbonyl)piperidine TFA salt (from Step A) in methylene chloride (1.5 mL) was added anisole (0.017 mL) and TFA (0.230 mL). After several h at rt, volatiles were removed under reduced pressure. Purification of the residue was done by preparative reverse-phase HPLC using a 9.4 x 250 mm Semi-preparative Zorbax SB-C18 column with a 15-25% acetonitrile gradient in water having 0.5% (v/v) TFA over 15 min at 6.0 mL per minute to give the title compound (40.7 mg) as a gel.

PROCEDURE 3

4-(4-(2-Phenyleth-1-yl)-1-ethyl-(1H)-pyrazol-5-yl)piperidine di-TFA salt

Step A: 4-Phenylbutyl bromide

To a solution of 4-phenyl-1-butanol (21.75 g) in acetonitrile (300 mL) was added triphenylphosphine dibromide (67.23 g) in portions with stirring over 10 min. After stirring over night under nitrogen, methanol (4 mL) was added and after 1.5 h, the solvent was removed under reduced pressure. Hexanes (200 mL) and ~75 g silica gel were added to the residue and the mixture was filtered and the filter cake was eluted with hexanes. The clear filtrate was concentrated to give 32.8 g of clear colorless liquid. This product was again eluted through silica gel using 1.5 L hexanes to give the title compound (24.7 g) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28-7.32 (m, 2 H), 7.20-7.23 (m, 3 H), 3.44 (t, J = 6.8 Hz, 2 H), 2.67 (t, J = 7.6 Hz, 2 H), 1.93-1.89 (m, 2 H), 1.77-1.84 (m, 2 H).

Step B: (4-Phenylbut-1-yl)triphenylphosphonium bromide A solution of 4-phenylbutyl bromide from the Step A (24.7 g) and triphenylphosphine (19.00 g) in toluene (100 mL) was heated at 120-130 °C for 3 days. The reaction was cooled to rt and the solid precipitate was collected by filtration, washed with toluene and air dried. The solid was dissolved in a 2:1 mixture of water and acetonitrile and gave the title compound (30.6 g) as a white solid after lyopholization.
^{1}H NMR (500 MHz, CD_3OD): δ 7.84-7.89 (m, 2 H), 7.71-7.81 (m, 15 H), 7.20-7.23 (m, 1 H), 7.11-7.15 (m, 2 H), 3.37-3.43 (m, 2 H), 2.66 (t, J = 7.5 Hz, 2 H), 1.87 (tt, J = 7.5 and 7.3 Hz, 2 H), 1.63-1.70 (m, 2 H).

Step C: 1-Benzyl-4-(4-phenylbutylidene)piperidine
A 0.62M solution of potassium bis(trimethylsilyl)amide in THF (180 mL, 112 mmol) in toluene (250 mL) was added to a mixture of (4-phenylbut-1-yl)triphenylphosphonium bromide from Step B (53 g) in toluene (250 mL) in an ice bath over 15 min with stirring under nitrogen. After stirring for a further 15 min, a solution of 1-benzyl-4-piperidone (16.9 g) in toluene (100 mL) was added over 30 min with stirring. The reaction mixture was allowed to warm to rt over 15 h. The reaction mixture was then poured into cold 1N HCl (400 mL) and the layers were separated. The organic layer was extracted with two more portions of 1N HCl. The combined cloudy HCl solution and an oil layer in between were washed with toluene (200 mL) before the aqueous layer was basified by the addition of potassium hydroxide (30 g). The aqueous layer was extracted with ether (3x150 mL) and the combined organic layers were washed with water and brine, dried over sodium sulfate and concentrated. The crude product was purified by FC (10-15% ethyl acetate in hexanes having 4% (v/v) TEA) to give the title compound (16 g) as a colorless oil. R_f: 0.47 (20% ethyl acetate in hexanes having 4% (v/v) TEA).
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26-7.38 (m, 7 H), 7.18-7.21 (m, 3 H), 5.18 (t, J = 7.4 Hz, 1 H), 3.54 (s, 2 H), 2.61-2.64 (m, 2 H), 2.42-2.49 (m, 4 H), 2.22-2.27 (m, 4 H), 2.02-2.07 (m, 2 H), 1.65-1.71 (m, 2 H).

Step D: 1-(1-Benzylpiperidin-4-yl)-4-phenylbutan-1-one

To a solution of 4-(4-phenylbutylidene)-1-benzylpiperidine from Step C (4.37 g) in anhydrous ether (150 mL) under nitrogen with stirring was add 1M borane solution in THF (45 mL). The reaction was stirred for 3 h when water (2 mL) was added dropwise. The mixture was stirred a further 30 min and was then cooled in an ice bath. A solution of chromic anhydride (2.5 g), concentrated sulfuric acid (5.44 mL) and water (125 mL) was added dropwise with vigorous magnetic stirring over 5 min. After another 5 min, the ice bath was removed. After 1.5 h at rt, 0.5N sodium hydroxide and ether (400 mL each) were added and the mixture was stirred until the residue dissolved. The layers were separated and the aqueous layer was extracted twice with ether. The combined ether layers were washed with an aqueous EDTA solution, water and brine (100 mL each), dried over sodium sulfate and concentrated under reduced pressure to give a colorless gel. Flash chromatography on silica gel with 30-50% ethyl acetate in hexanes with 3% (v/v) TEA gave the title compound (1 g) as a colorless gel. R_f: 0.43 (30% ethyl acetate in hexanes with 3% (v/v) TEA). ^1H NMR (500 MHz, $CDCl_3$): δ 7.25-7.33 (m, 7 H), 7.16-7.22 (m, 3 H), 3.51 (s, 2 H), 2.89-2.93 (m, 2 H), 2.63 (t, J = 7.6 Hz, 2 H), 2.46 (t, J = 7.2 Hz, 2 H), 2.38 (tt, J = 11.5 and 3.9 Hz, 1 H), 1.99-2.03 (m, 2 H), 1.92 (tt, J = 7.2 and 7.6 Hz, 2 H), 1.76-1.81 (m, 2 H), 1.65-1.72 (m, 2 H).

Step E: 1-(1-Benzylpiperidin-4-yl)-2-formyl-4-phenylbutan-1-one

To a solution of potassium t-butoxide (0.673 g) in THF (20 mL) under nitrogen and cooled in an ice bath was added a solution of 1-(1-benzylpiperidin-4-yl)-4-phenylbutan-1-one from Step D (0.71 g) and methyl formate (3.76 mL) in THF (12 mL) over 5 minute. The reaction was stirred for 15 min before being allowed to warm to rt for 2 h. The reaction was poured into water and extracted with ether (4 x 100 mL), methylene chloride (100 mL), and THF (100 mL). The combined organic layers were washed with water and brine, dried over sodium sulfate and concentrate under reduced pressure. The crude product was purified by FC on silica gel eluting with 5 and 20% methanol in ethyl acetate with 4% TEA to afford the title compound (0.8 g). ^1H NMR (500 MHz, $CDCl_3$) showed a 3:1 ratio of enol (δ 8.54 ppm) and aldehyde (δ 9.54 ppm) forms. Other signals from the two forms were only partially resolved. The title compound had a retention time of 9.47 min on a Zorbax SB-C18 column (4.6x75 mm) eluting with 20-100% gradient of acetonitrile in water with 0.1% TFA over 10 min at 1 mL per min.

Step F: 4-(4-(2-Phenyleth-1-yl)-1-ethyl-(1H)-pyrazol-5-yl)-1-benzylpiperidine di-TFA salt A solution of 1-(1-benzylpiperidin-4-yl)-2-formyl-4-phenyl-1-butanone from Step E (76.5 mg) and ethylhydrazine oxalate (45 mg) in methanol (4 mL) was heated at 45 °C for 15.5 h. The solvent was removed under reduced pressure. The residue was purified by preparative reverse-phase HPLC using a 9.4x250 mm Semi-preparative Zorbax SB-C18 column with 30-50% acetonitrile gradient in water having 0.5% (v/v) TFA over 15 min at 7.1 mL per min to give the title compound (45 mg) as the faster-eluting, minor isomer.

^{1}H NMR (500 MHz, CD_3OD): δ 7.46-7.52 (m, 5 H), 7.37 (s, 1 H), 7.21-7.24 (m, 2 H), 7.12-7.15 (m, 3 H), 4.32 (s, 2 H), 4.17 (q, J = 7.2 Hz, 2 H), 3.53 (br d, J = 12.4 Hz, 2 H), 3.06-3.12 (m, 3 H), 2.79-2.88 (m, 4 H), 2.10-2.20 (m, 2 H), 1.78 (br d, J = 14.2 Hz, 2 H), 1.34 (t, J = 7.2 Hz, 3 H). The isomeric assignment was confirmed by a NOESY spectrum.

HPLC/MS (ESI): m/z 374.3 (M + 1), 2.51 min.

Step G: 4-(4-(2-Phenyleth-1-yl)-1-ethyl-(1H)-pyrazol-5-yl)piperidine di-TFA salt A mixture of ammonium formate (119 mg), 20% $Pd(OH)_2/C$ (5 mg) and 4-(4-(2-phenylethyl)-1-ethyl-(1H-pyrazol-5-yl))-1-benzylpiperidine di-TFA salt from Step F in methanol (2 mL) was heated at 60 °C for 1.5 h. The solvent was removed under reduced pressure and the residue was purified by preparative reverse-phase HPLC using a 9.4x250 mm Semi-preparative Zorbax SB-C18 column with 20-35% acetonitrile gradient in water having 0.5% (v/v) TFA over 15 min at 6.25 mL per min to give the title compound as the di-TFA salt (25 mg) as a gel.

^{1}H NMR (500 MHz, CD_3OD): δ 7.40 (s, 1 H), 7.22-7.25 (m, 2 H), 7.13-7.17 (m, 3 H), 4.20 (q, J = 7.3 Hz, 2 H), 3.42-3.46 (m, 2 H), 3.05-3.15 (m, 3 H), 2.83-2.90 (m, 4 H), 2.04-2.14 (m, 2 H), 1.74-1.79 (m, 2 H), 1.36 (t, J = 7.4 Hz, 3 H). The isomer assignment was confirmed by an NOE difference spectrum.

PROCEDURE 4A

4-(3-(4-Fluorobenzyl)-1-ethyl-(1H)-pyrazol-5-yl)piperidine di-TFA

The title compound was prepared using essentially the same procedure as that described in Procedure 1, but substituting methyl 4-fluorophenylacetate for methyl phenylacetate in Step A, Method B, Step B3.

PROCEDURE 4B

4-(3-(3,4-Difluorobenzyl)-1-ethyl-(1H)-pyrazol-5-yl)piperidine di-TFA

The title compound was prepared using essentially the same procedure as that described in Procedure 1, but substituting methyl 3,4-difluorophenylacetate for methyl phenylacetate in Step A, Method B.

PROCEDURE 5

4-(3-(Benzofurazan-4-yl)prop-1-yl)piperidine hydrochloride

Step A: (1-t-Butoxycarbonylpiperidin-4-yl)acetaldehyde A solution of oxalyl chloride (1.23 mL, 14.1 mmol) in methylene chloride (50 mL) was cooled to -78 °C. DMSO (2.0 mL, 28.3 mmol), was added slowly via syringe. After 10 min, 4-(2-hydroxyeth-1-yl)-1-t-butoxycarbonylpiperidine (2.7 g, 11.8 mmol) in methylene chloride (15 mL) was added. The cold mixture was stirred for an additional 20 min then TEA (8.2 mL, 59 mmol) was added. The mixture was warmed to rt and stirred for 1.5 h, then diluted with methylene chloride (300 mL). The organic phase was washed with 1M sodium hydroxide, dried over sodium sulfate and concentrated. FC (125 g silica, 2.5/1 hexanes/ethyl acetate) afforded the title compound (2.25 g).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.1-1.2 (m, 2 H), 1.45 (s, 9 H), 1.65-1.75 (m, 2 H), 1.99-2.13 (m, 1 H), 2.38-2.4 (d, 2 H), 2.65-2.8 (m, 2 H), 4.03-4.15 (m, 2 H), 9.78 (s, 1 H)

Step B: 4-(Prop-2-en-1-yl)-1-t-butoxycarbonylpiperidine

A solution of methyltriphenylphosphonium bromide (5.3 g, 14.8 mmol) in THF (50 mL) was cooled to 0 °C under nitrogen. Potassium hexamethyl disilazide (27.7 mL, 0.5M toluene solution, 13.9 mmol) was added and the mixture was stirred for 30 min. A solution of (1-t-butoxycarbonylpiperidin-4-yl)acetaldehyde from Step A (2.25 g, 9.9 mmol) in THF (10 mL) was added and the mixture was warmed to rt. After 30 min, the reaction was complete by tlc analysis. The mixture

was diluted with ethyl acetate (200 mL) and washed with water and brine (100 mL each). The organic phase was dried over sodium sulfate and concentrated to give an oil which was purified by FC (75 g silica, 10/1 hexane/ethyl acetate) to afford the title compound (1.61 g).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.03-1.18 (m, 2 H), 1.45 (s, 9 H), 1.4-1.5 (m, 1 H), 1.6-1.7 (m, 2 H), 1.99-2.13 (t, 1 H), 2.62-2.75 (m, 2 H), 4.03-4.15 (m, 2 H), 4.98-5.12 (m, 2 H), 5.7-5.83 (m, 1 H).

Step C: 4-Bromobenzofurazan

To a solution of 2,6-dibromoaniline (10 g, 40 mmol) in glacial acetic acid (160 mL) was added 30% hydrogen peroxide (30 mL). The mixture was left for 48 h at which point crystals had precipitated. The crystals were collected by filtration, washed with acetic acid and water then dried under high vacuum to give 2,6-dibromonitrosobenzene (6.24 g). This material (2.6 g, 10 mmol) was dissolved in DMSO (25 mL) along with sodium azide (650 mg, 10 mmol). The mixture was heated to 100 °C for 1 h then cooled to rt and diluted with ethyl acetate and water. The layers were separated and the organic phase was washed with water and brine, then dried over sodium sulfate and concentrated. FC (75 g silica, 10/1 hexane/ethyl acetate) afforded the title compound (1.7 g).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25-7.35 (dd, 1 H), 7.6-7.65 (d, 1 H), 7.78-7.82 (d, 1 H)

Step D: 4-(3-(Benzofurazan-4-yl)prop-1-yl)piperidine hydrochloride

A solution of 4-(prop-2-en-1-yl)-1-t-butoxycarbonylpiperidine from Step B (330 mg, 1.46 mmol) in dry THF (0.5 mL) was cooled to 0 °C and a solution of 9-BBN (3.2 mL, 0.5 M in THF, 1.61 mmol) was added. The mixture was warmed to rt and stirred for 5 h. Potassium carbonate (405 mg, 2.93 mmol), 1,2-bis(diphenylphosphino)-ferrocenyl palladium dichloride (60 mg, 0.073 mmol) and 4-bromobenzofurazan (from Step C) (292 mg, 1.46 mmol) were added followed by dry DMF (5 mL). The resulting mixture was heated to 55 °C overnight then diluted with ethyl acetate. The solution was washed with water (3x) and brine, then dried over sodium sulfate and concentrated. FC (15 g silica, 5/1 hexane/ethyl acetate) afforded the title Boc derivative. Heating in 1% conc. HCl/methanol at 50 °C for 2 h followed

by removal of solvent and drying under vacuum afforded the title compound as the hydrochloride (155 mg).
^{1}H NMR (300 MHz, CD_3OD): δ 1.31-1.42 (m, 4 H), 1.6-1.75 (m, 1 H), 1.84-2.0 (m, 4 H), 2.9-3.1 (m, 4 H), 3.3-3.4 (m, 2 H), 7.25-7.3 (d, 1 H), 7.4-7.5 (dd, 1 H), 7.7-7.75 (d, 1 H).

PROCEDURE 6

4-(3-(Benzofurazan-5-yl)prop-1-yl)piperidine hydrochloride

Using essentially the same methods as in Procedure 5, but substituting 2,5-dibromoaniline for 2,6-dibromoaniline in Step C, the title compound was prepared.

PROCEDURE 7

4-(3-(4-Cyanophenyl)prop-1-yl)piperidine hydrochloride

Starting with 4-(prop-2-en-1-yl)-1-t-butoxycarbonylpiperidine from Procedure 5, Step B (475 mg, 2.1 mmol) and using essentially the same methods as in Procedure 5, Step D, but substituting 4-bromobenzonitrile (382 mg, 2.1 mmol), the title compound (337 mg) was obtained as the hydrochloride.
^{1}H NMR (300 MHz, CD_3OD). δ 1.31-1.42 (m, 4 H), 1.58-1.75 (m, 5 H), 1.9-2.1 (m, 2 H), 2.67-2.77 (t, 2 H), 2.9-3.0 (m, 2 H), 3.3-3.4 (m, 2 H), 7.35-7.4 (d, 2 H), 7.6-7.63 (d, 2 H).

PROCEDURE 8

4-(3-(4-Cyano-3-fluorophenyl)prop-1-yl)piperidine hydrochloride

Starting with 4-(prop-2-en-1-yl)-1-t-butoxycarbonylpiperidine from Procedure 5, Step B and using essentially the same methods as in Procedure 5, Step D, but substituting 4-bromo-2-fluorobenzonitrile, the title compound was obtained as the hydrochloride.

PROCEDURE 9

4-(3-(4-Fluorophenyl)prop-1-yl)piperidine hydrochloride

Starting with 4-(prop-2-en-1-yl)-1-t-butoxycarbonylpiperidine (from Procedure 5, Step B) and using essentially the same methods as in Procedure 5, Step D, but substituting 4-bromofluorobenzene, the title compound was obtained as the hydrochloride.

PROCEDURE 10

4-(3-(Quinolin-3-yl)propyl)piperidine di-hydrochloride salt

Step A: 1-(t-Butoxycarbonyl)-4-(3-(quinolin-3-yl)propyl)piperidine

A solution of 1-(t-butoxycarbonyl)-4-(prop-2-en-1-yl)piperidine (from Procedure 5, Step B) (260 mg, 1.15 mmol) in THF (3 mL) under argon was treated with 0.5M 9-BBN solution in THF (2.30 mL, 1.15 mmol). The resulting mixture was stirred at rt for 2 h, then treated with sodium methoxide (68 mg, 1.25 mmol). The resulting mixture was stirred until it was homogeneous (~15 min) and then was treated with 3-(bromo) quinoline (0.155 mL, 1.15 mmol) and [1,1'-bis(triphenylphosphino)ferrocene)dichloropalladium · methylene chloride (41 mg, 0.05 mmol). The resulting mixture was heated at reflux for 30 min, cooled and quenched with 1N NaOH (20 mL). The quenched reaction was extracted with 2 x 50 mL of ether; the extracts were dried over magnesium sulfate, combined and concentrated. FC (15 g of silica gel, 4:1 v/v hexanes/ethyl acetate) afforded the title compound (240 mg).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.00-1.16 (m, 2 H), 1.25-1.40 (m, 2 H), 1.45 (s, 9 H), 1.60-1.80 (m, 5 H), 2.62-2.72 (m, 2 H), 2.79 (t, J = 7.8, 2 H), 4.06 (br s, 2 H), 7.52 (m, 1 H), 7.66 (m, 1 H), 7.76 (dd, J = 8.0, 1.6, 1 H), 7.91 (d, J = 1.6, 1 H), 8.77 (d, J = 2.2, 1 H).

Step B: 4-(3-(Quinolin-3-yl)propyl)piperidine di-hydrochloride salt

A solution of 1-(t-butoxycarbonyl)-4-(3-(quinolin-3-yl)propyl)piperidine from Step A (240 mg, 0.68 mmol) in 1M HCl solution (8 mL) in methanol was stirred at rt for 48 h. The solution was concentrated and the residue crystallized from ethyl acetate to afford the title compound (182 mg),

^{1}H NMR (500 MHz, CD_3OD): δ 1.37-1.49 (m, 4 H), 1.67-1.74 (m, 2 H), 1.85-1.91 (m, 2 H), 1.99 (app d, J = 13.5 Hz, 2 H), 2.99 (app t, J = 11.5 Hz, 2 H), 3.05 (t, J = 8.0 Hz, 2 H), 3.38 (app d, J = 12.5 Hz, 1 H), 7.97 (t, J = 7.0 Hz, 1 H), 8.13 (dt. J = 1.0 and

7.0 Hz, 1H), 8.24 (d, J = 8.5 Hz, 1 H), 8.31 (d, J = 8.0 Hz, 1 H), 9.10 (s, 1 H), 9.21 (d, J = 1.0 Hz, 1 H).

PROCEDURE 11

4-(3-(2-Pyridyl)propyl)piperidine di-TFA salt

Step A: 1-(t-Butoxycarbonyl)-4-(3-(2-pyridyl)propyl)piperidine

The title compound was prepared using a procedure analogous to that described in Procedure 10, Step A, substituting (2-bromo)pyridine for (3-bromo)quinoline. FC (4:1 v/v hexanes/ethyl acetate followed by 3:2 v/v hexanes/ethyl acetate) provided the title compound (135 mg, 48%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.05-1.81 (m, 10 H), 1.46 (s, 9 H), 2.67-2.82 (m, 2 H), 3.65 (m, 1 H), 4.08-4.16 (m, 2 H), 7.14-7.18 (m, 2 H), 7.63 (m, 1 H), 8.54 (d, J = 4.4 Hz, 1 H).

HPLC/MS (ESI): m/z 304 (M+1).

Step B: 4-(3-(2-Pyridyl)propyl)piperidine di-TFA salt

To a solution of 1-(t-butoxycarbonyl)-4-(3-(2-pyridyl)propyl)piperidine (from Step A) (128 mg, 0.42 mmol) in methylene chloride (1 mL) was added TFA (1 mL). After stirring for 2 h at rt, the reaction was concentrated to give the title compound (36 mg).

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.22-1.46 (m, 5 H), 1.73-1.79 (m, 4 H), 2.68 (t, J = 11.8 Hz, 2 H), 2.78 (t, J = 7.8 Hz, 2 H), 3.19 (d, J = 11.8 Hz, 2 H), 5.32 (br s, 1 H), 7.09-7.15 (m, 2 H), 7.59 (t, J = 7.7 Hz, 2 H), 8.52 (d, J = 4.6 Hz, 1 H).

PROCEDURE 12

4-(3-(4-(Trifluoromethyl)pyrimidin-2-yl)propyl)piperidine

Step A: 1-(t-Butoxycarbonyl)-4-(3,3-dibromoprop-2-en-1-yl)piperidine

To a solution of carbon tetrabromide (286 mg, 0.86 mmol) in methylene chloride (4 mL) at –10 °C was added triphenylphosphine (339 mg, 1.29 mmol). After 10 min, a solution of ((1-t-butoxycarbonyl)piperidin-4-yl)acetaldehyde (from Procedure 5, Step A) (98 mg, 0.43 mmol) and TEA (0.060 mL, 0.43 mmol) in methylene chloride (2 mL) was added. After stirring at rt for 2 h, the reaction mixture

was concentrated. The residue was purified by FC (9:1 v/v hexanes/ethyl acetate followed by 1:1 v/v hexanes/ethyl acetate) to give the title compound (118 mg).
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.14-1.22 (m, 2 H), 1.47 (s, 9 H), 1.57-1.60 (m, 1 H), 1.67 (br d, J = 12.6 Hz, 2 H), 2.08 (t, J = 7.1 Hz, 2 H), 2.70 (t, J = 12.7 Hz, 2 H), 4.10 (br d, J = 12.6 Hz, 2 H), 6.42 (t, J = 7.4 Hz, 1 H).

Step B: 1-(t-Butoxycarbonyl)-4-(prop-2-yn-1-yl)piperidine

To a solution of 118 mg (0.31 mmol) of 1-(t-butoxycarbonyl)-4-(3,3-dibromoprop-2-en-1-yl)piperidine from Step A in THF (4 mL) at –78 °C was added a 2.5M solution of n-butyl lithium (0.370 mL, 0.92 mmol). After stirring at –78 °C for 45 min, the reaction mixture was quenched with sat'd ammonium chloride (4 mL) and diluted with ether (25 mL). After separating the phases, the aqueous layer was extracted with ether. The combined organic phases were washed with brine, dried over magnesium sulfate and concentrated. The residue was purified by FC (4:1 v/v hexanes/ether) to give the title compound (55 mg).
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.18-1.26 (m, 2 H), 1.47 (s, 9 H), 1.60-1.67 (m, 1 H), 1.77 (br d, J = 13.2 Hz, 2 H), 1.99 (t, J = 2.6 Hz, 1 H), 2.16 (dd, J = 6.6 Hz, 2.5, 2 H), 2.68-2.74 (m, 2 H), 4.12 (br d, J = 13.0 Hz, 2 H).

Step C: 1-(t-Butoxycarbonyl)-4-(3-((4-trifluoromethyl)pyrimidin-2-yl)prop-2-yn-1-yl)piperidine

To a solution of 1-(t-butoxycarbonyl)-4-(prop-2-yn-1-yl)piperidine from Step B (86 mg, 0.39 mmol) in TEA (4 mL) under argon at 0 °C was added 2-chloro-4-(trifluoromethyl)pyrimidine (0.070 mL, 0.58 mmol). After stirring at 0 °C for 5 min, dichlorobis(triphenylphosphine)palladium(II) (27 mg, 0.04 mmol), and copper iodide (4 mg, 0.02 mmol) was added and the reaction vessel was flushed with argon. After 3 h at 60 °C, the reaction mixture was cooled to rt and quenched with 1N sodium hydroxide (5 mL) and diluted with ether (25 mL). After separating the phases, the aqueous layer was extracted again with ether. The combined organic phases were washed with brine, dried over magnesium sulfate and concentrated. The residue was purified by FC (9:1 v/v hexanes/ethyl acetate followed by 2:1 v/v hexanes/ethyl acetate) to give the title compound (132 mg).
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26-1.33 (m, 2 H), 1.46 (s, 9 H), 1.80-1.88 (m, 3 H), 2.46 (d, J = 6.4 Hz, 2 H), 1.99 (br t, J = 11.2 Hz, 1 H), 4.10-4.40 (m, 2 H), 7.54 (d, J = 5.0 Hz, 1 H), 8.94 (d, J = 5.0 Hz, 1 H).

Step D: 1-(t-Butoxycarbonyl)-4-(3-((4-trifluoromethyl)pyrimidin-2-yl)prop-1-yl)piperidine

To a solution of 1-(t-butoxycarbonyl)-4-(3-((4-trifluoromethyl)pyrimidin-2-yl)prop-2-yn-1-yl)piperidine from Step C (130 mg) in methanol (4 mL) was added 10% palladium on carbon (15 mg). The mixture was hydrogenated using a Parr shaker set at 40 psi. After TLC indicated the absence of the starting material, the reaction was filtered through a 0.45 micron nylon membrane polypropylene filter and concentrated. FC (9:1 v/v hexanes/ethyl acetate followed by 2:1 v/v hexanes/ethyl acetate) of the residue afforded the title compound.
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.04-1.15 (m, 2 H), 1.27-1.49 (m, 3 H), 1.46 (s, 9 H), 1.68 (br d, J = 12.7 Hz, 2 H), 1.85-1.93 (m, 2 H), 2.68 (br t, J = 12.1 Hz, 2 H), 3.05 (t, J = 7.7 Hz, 2 H), 4.08 (br d, J = 11.5 Hz, 2 H), 7.47 (d, J = 5.0 Hz, 1 H), 8.92 (d, J = 5.0 Hz, 1 H).

Step E: 4-(3-((4-Trifluoromethyl)pyrimidin-2-yl)prop-1-yl)piperidine

The title compound was prepared from 1-(t-butoxycarbonyl)-4-(3-((4-trifluoromethyl)pyrimidin-2-yl)prop-1-yl)piperidine (from Step D) (17 mg, 0.046 mmol) using a procedure analogous to that described in Procedure 10, Step B. FC (95:5:0.5 v/v/v methylene chloride/methanol/ NH_4OH) afforded the title compound (22 mg).
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.21-3.45 (m, 15 H), 7.52 (d, J = 5.0 Hz, 1 H), 8.95 (d, J = 5.0 Hz, 1 H).

PROCEDURE 13

4-(*N*-(Pyrimidin-2-yl)-*N*-(prop-1-yl)amino)piperidine di-hydrochloride salt

Step A: 4-Amino-1-t-butoxycarbonylpiperidine

1-t-Butoxycarbonylpiperidin-4-one (20 g, 100 mmol), benzylamine (11 mL, 100 mmol) and sodium triacetoxyborohydride (32 g, 150 mmol) were stirred together in 1,2-dichloroethane (400 mL) for 3 h. The resulting mixture was diluted with ethyl acetate (1 L) and washed with 1M aqueous sodium hydroxide (500 mL) followed by brine (500 mL). The organic phase was dried over sodium sulfate and concentrated to afford 4-*N*-benzylamino-1-t-butoxycarbonyl piperidine (30.1 g) as a

viscous oil. The oil was dissolved in methanol (400 mL) and ammonium formate (39 g, 600 mmol) was added. The vessel was purged with nitrogen and 10% palladium on carbon (6.5 g, 6 mmol) was added. The mixture was refluxed for 1 h and then filtered through celite and concentrated. Drying under vacuum afforded the title compound (20 g).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.15-1.3 (m, 2 H), 1.43 (s, 9 H), 1.7-1.9 (m, 4 H), 2.65-2.72 (m, 3 H), 3.95-4.1 (m, 2 H).

Step B: 4-(*N*-(Pyrimidin-2-yl)amino)-1-t-butoxycarbonylpiperidine

4-Amino-1-t-butoxycarbonylpiperidine from Step A, (1.9 g, 9.5 mmol), 2-chloropyrimidine (1.1 g, 9.5 mmol) and DIPEA (3.3 mL, 19 mmol) were combined in isopropanol (10 mL) and the mixture was refluxed for 24 h. The mixture was cooled, diluted with methylene chloride (100 mL) and washed with water and brine. The organic phase was dried over sodium sulfate and concentrated. FC (60 g silica, 1/1 hexanes/ethyl acetate) afforded the title compound (0.97 g).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.31-1.45 (m, 2 H), 1.44 (s, 9 H), 2.0-2.1 (m, 2 H), 2.9-3.0 (m, 2 H), 3.9-4.1 (m, 3 H), 5.0-5.05 (m, 1 H), 6.5-6.58, (t, 1 H), 8.15-8.2 (d, 2 H).

Step C: 4-(*N*-(Pyrimidin-2-yl)-*N*-(allyl)amino)-1-t-butoxycarbonylpiperidine

A solution of 4-(*N*-(pyrimidin-2-yl)amino)-1-t-butoxycarbonylpiperidine from Step B (528 mg, 1.9 mmol) in dry THF (5 mL) was cooled to -78 °C and a solution of sodium hexamethyldisilazide (2.8 mL, 1.0 M in THF, 2.8 mmol) was added via syringe. The mixture was stirred cold for 20 min then allyl bromide (0.23 mL, 2.7 mmol) was added. The mixture was then warmed to rt and stirred for 1.5 h at which time TLC showed very little starting material. The solution was poured into sat'd ammonium chloride and methylene chloride. The layers were separated and the organic phase was dried over sodium sulfate and concentrated. FC (25 g silica, 4/1 hexanes/ethyl acetate) afforded the title compound (367 mg).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.45 (s, 9 H), 1.6-1.8 (m, 4 H), 2.75-2.85 (m, 2 H), 4.1-4.3 (m, 4 H), 4.7-4.8 (m, 1 H), 5.05-5.17 (m, 2 H), 5.92-5.98 (m, 1 H), 6.45-6.5 (t, 1 H), 8.3-8.35 (d, 2 H).

Step D: 4-(*N*-(Pyrimidin-2-yl)-*N*-(prop-1-yl)amino)piperidine di-hydrochloride salt

In a round bottom flask purged with nitrogen 4-(*N*-(pyrimidin-2-yl)-4-N-(allyl)amino)-1-t-butoxylcarbonylpiperidine from Step C (461 mg, 1.45 mmol) was dissolved in methanol (4 mL) and 10% palladium on carbon (150 mg, 0.14 mmol) was added. The mixture was stirred under 1 atm of hydrogen using a balloon for 1.5 h. The mixture was filtered through celite and concentrated. FC (20 g silica, 3/1 hexanes/ethyl acetate) afforded 4-(*N*-(pyrimidin-2-yl)-4-*N*-(prop-1-yl)amino)-1-t-butoxylcarbonylpiperidine.

^{1}H NMR (400 MHz, $CDCl_3$). δ 0.9-1.0 (t, 3 H, J=7 Hz), 1.5 (s, 9 H), 1.6-1.8 (m, 6 H), 2.8-2.9 (m, 2 H), 3.33-3.4 (m, 2 H), 4.2-4.27 (m, 2 H), 4.7-4.8 (m, 1 H), 6.42-6.45 (t, 1 H),), 8.3-8.35 (d, 2 H).

This material was dissolved in 2 % conc. HCl/methanol and heated to 50 °C for 2 h. Removal of solvent and drying under vacuum afforded the title compound as a white solid.

PROCEDURE 14

4-(3-(3,4-Difluorophenyl)prop-1-yl)piperidine hydrochloride salt

Starting with 4-(prop-2-en-1-yl)-1-t-butoxycarbonylpiperidine from Procedure 5, Step B and using essentially the same methods as in Procedure 5, Step D, but substituting 3,4-difluorobromobenzene, the title compound was obtained as the hydrochloride.

PROCEDURE 15

4-(5-Benzyl-1-(prop-1-yl)-(1H)-pyrazol-3-yl)piperidine di-hydrochloride salt (Higher R_f isomer) and 4-(3-benzyl-1-(prop-1-yl)-(1H)-pyrazol-5-yl)piperidine di-hydrochloride salt (Lower R_f isomer)

Using essentially the same methods as in Procedure 1, Step B-C, but substituting propylhydrazine for ethylhydrazine in Step B, the title compounds were prepared.

PROCEDURE 16

4-(3,3-Difluoro-3-phenylprop-1-yl)piperidine

Step A: 1-(Benzyloxycarbonyl)-4-(3-oxo-3-phenylprop-1-en-1-yl)piperidine

DIPEA (4.6 mL, 3.4 g, 26 mmol) was added to a solution of 4-(hydroxymethyl)piperidine (2.00 g, 17.4 mmol) dissolved in methylene chloride (20 mL). The solution was cooled in an ice bath and benzyl chloroformate (2.5 mL, 3.0 g, 18 mmol) was added dropwise over 10 min. After warming to rt and stirring for 96 h, the mixture was diluted with ethyl acetate (50 mL) and washed in succession with 25 mL each of saturated aq. sodium bicarbonate, 2N aq. HCl, saturated aq. sodium bicarbonate, and saturated aq. brine. The organic layer was dried (sodium sulfate), decanted, and evaporated to give 4.14 g of 1-(benzyloxycarbonyl)-4-(hydroxymethyl)piperidine.

1,1,1-Triacetoxy-1,1-dihydro-1,2-benzoiodoxol-3(1H)-one (1.92 g, 4.53 mmol) was added to a solution of 1-(benzyloxycarbonyl)-4-(hydroxymethyl)piperidine (1.00 g, 4.01 mmol) in methylene chloride (20 mL) and the mixture was stirred at rt for 45 min. Ether (75 mL) and 1.3 N aq. NaOH (25 mL) were added and stirring was continued for 15 min. The mixture was transferred to a separatory funnel with additional ether (30 mL) and 1.3 N aq. NaOH (20 mL). The organic layer was separated, washed with saturated aq. brine (20 mL), dried (sodium sulfate), decanted, and evaporated to give 846 mg of 1-(benzyloxycarbonyl)-4-piperidine carboxaldehyde as a colorless syrup.

Diethyl (2-oxo-2-phenylethyl)phosphonate (0.96 mL, 1.1 g, 4.4 mmol) was added in one portion to a stirred suspension of sodium hydride (60% oil dispersion, 158 mg, 3.95 mmol) in THF (20 mL). After 15 min. at rt, the clear solution was cooled in an ice bath and 1-(benzyloxycarbonyl)-4-piperidinecarboxaldehyde (840 mg, 3.40 mmol) was added in THF (1.0 mL) with additional THF (2 x 1.0 mL) for rinsing. Stirring was continued for a total of 2 h, with slow warming to rt. The mixture was then partitioned between ether (120 mL) and 2.5 N aq. NaOH (60 mL). The organic layer was washed with saturated aq. brine (60 mL), dried (sodium sulfate), decanted, and evaporated. The crude product was purified by FC, eluting with 15-20% ethyl acetate in hexane, to give 0.95 g of the title compound as a colorless syrup.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, J = 8 Hz, 2 H), 7.57 (t, J = 8 Hz, 1 H), 7.48 (t, J = 8 Hz, 2 H), 7.39-7.29 (m, 5 H), 6.99 (dd, J = 15, 6 Hz, 1 H), 6.87 (dd, J = 15

and 1 Hz, 1 H), 5.15 (s, 2 H), 2.97-2.82 (m, 2 H), 2.50-2.39 (m, 1 H), 1.89-1.77 (m, 2 H), 1.54-1.39 (m, 2 H).
MS (ESI): m/z 367 (M + NH_3 + H).

Step B: 2-(2-(1-(Benzyloxycarbonyl)piperidin-4-yl)ethyl)-2-phenyl-1,3-dithiolane

1-(Benzyloxycarbonyl)-4-(3-oxo-3-phenylprop-1-en-1-yl)piperidine from Step A (0.95 g, 2.7 mmol) was hydrogenated using 5% Pd/C (10 mg) in 95% ethanol (20 mL) at atmospheric pressure. After 3.5 h, the mixture was filtered and the catalyst was washed with 95% ethanol. Evaporation of the filtrate gave 0.95 g of 1-(benzyloxycarbonyl)-4-(3-oxo-3-phenylprop-1-yl)piperidine as a colorless syrup.

Boron trifluoride-acetic acid complex (BF_3·2-CH_3CO_2H, 0.370 mL, 501 mg, 2.67 mmol) was added to a solution of 1,2-ethanedithiol (0.440 mL, 494 mg, 5.25 mmol) and (1-(benzyloxycarbonyl)-4-(3-oxo-3-phenylprop-1-yl)piperidine (930 mg, 2.65 mmol) in methylene chloride (4.0 mL) at rt. After 6 h, the mixture was diluted with ether (50 mL) and washed with saturated aq. sodium bicarbonate (2 x 25 mL), 2.5 N aq. NaOH (25 mL), and saturated aq. brine (25 mL). The organic layer was dried (sodium sulfate), decanted, and evaporated. The crude product was purified by FC, eluting with 10% ethyl acetate in hexane, to give 1.05 g of the title compound as a colorless liquid.
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, J = 8 Hz, 2 H), 7.38-7.26 (m, 7 H), 7.22 (t, J = 8 Hz, 1 H), 5.10 (s, 2 H), 4.18-4.02 (m, 2 H), 3.41-3.32 (m, 2 H), 3.29-3.20 (m, 2 H), 2.79-2.62 (m, 2 H), 2.40-2.32 (m, 2 H), 1.65-1.54 (m, 2 H), 1.40-1.27 (m, 1 H), 1.24-1.16 (m, 2 H), 1.10-0.97 (m, 2 H);
HPLC/MS (ESI): m/z 428 (M + H); HPLC: 4.21 min.

Step C: 1-(t-Butoxycarbonyl)-4-(3,3-difluoro-3-phenylprop-1-yl)piperidine

1,3-Dibromo-5,5-dimethylhydantoin (74 mg, 0.26 mmol) was stirred with methylene chloride (0.50 mL) at rt, and the suspension was then cooled in a dry ice/isopropanol bath. After 5 min., hydrogen fluoride·pyridine (70% HF, 0.18 mL) was added over 1 min. After 5 min., a solution of 2-(2-(1-(benzyloxycarbonyl)piperidin-4-yl)ethyl)-2-phenyl-1,3-dithiolane from Step B (100 mg, 0.234 mmol) in methylene chloride (0.20 mL) was added over 1 min. After 10 min, the reaction mixture was diluted into methylene chloride (25 mL) and washed

with water (10 mL) containing sodium bisulfite (0.5 g). The organic layer was washed with saturated aq. sodium bicarbonate (2 x 10 mL) followed by saturated aq. brine (10 mL), dried (sodium sulfate), decanted, and evaporated to give 98 mg of colorless syrup. This material was combined with 195 mg of crude product from two similar reactions and purified by FC, eluting with 8% ethyl acetate in hexane, to give 247 mg of 1-(benzyloxycarbonyl)-4-(3,3-difluoro-3-phenylprop-1-yl)piperidine (R_f: 0.3 using 10% ethyl acetate in hexane) containing some residual impurity. .

The partially purified 1-(benzyloxycarbonyl)-4-(3,3-difluoro-3-phenylprop-1-yl)piperidine (247 mg) was hydrogenated at atmospheric pressure in 95% ethanol (4.0 mL) containing 20% $Pd(OH)_2/C$ (60 mg). After 6 h, additional 20% $Pd(OH)_2/C$ (32 mg) was added and the hydrogenation was continued for another 16 h. The mixture was filtered and the catalyst was washed with 95% ethanol. Evaporation of the filtrate gave 164 mg of crude 4-(3,3-difluoro-3-phenylprop-1-yl)piperidine as a colorless syrup.

Di-t-butyl dicarbonate (178 mg, 0.816 mmol) was transferred with methylene chloride (2 x 0.5 mL) to a solution of crude 4-(3,3-difluoro-3-phenylprop-1-yl)piperidine (164 mg) in methylene chloride (2.0 mL). After stirring at rt for 1 h, the solution was stored at -20 °C for 48 h. The mixture was then diluted into ethyl acetate (25 mL) and washed with saturated aqueous sodium bicarbonate (10 mL) followed by saturated aqueous brine (10 mL). The organic layer was dried (sodium sulfate), decanted, and evaporated. The crude product was purified by FC, eluting with 4-5% ethyl acetate in hexane to give the title compound as 112 mg of colorless syrup. R_f: 0.25 (5% ethyl acetate in hexane).

^1H NMR (400 MHz, $CDCl_3$): δ 7.50-7.40 (m, 5 H), 4.24-3.99 (m, 2 H), 2.64 (bt, J = 12 Hz, 2 H), 2.14 (tm, J = 16 Hz, 2 H), 1.62 (bd, J = 12 Hz, 2 H), 1.45 (s, 9 H), 1.42-1.33 (m, 3 H), 1.13-1.00 (m, 2 H).

Step D: 4-(3,3-Difluoro-3-phenylprop-1-yl)piperidine

Trifluoroacetic acid (2.5 mL, 3.7 g, 32 mmol) was added dropwise to a solution of 1-(t-butoxycarbonyl)-4-(3,3-difluoro-3-phenylprop-1-yl)piperidine from Step C (42 mg, 0.12 mmol) in methylene chloride (2.5 mL) at 0 °C. After 80 min., the solution was transferred using a double-ended needle to a rapidly stirred solution of sodium bicarbonate (5.0 g, 60 mmol) in water (50 mL). Ether (50 mL) and 2.5 N aq. NaOH (20 mL) were added, followed by solid brine to saturate the aqueous layer.

The aqueous layer was separated and extracted with ether (50 mL). The organic layers were washed in succession with saturated aq. brine (20 mL), combined, dried (sodium sulfate), decanted, and evaporated to give the title compound as 27 mg of colorless oil.

^{1}H NMR (400 MHz, CD_3OD): δ 7.51-7.40 (m, 5 H), 2.98 (dm, J = 12 Hz, 2 H), 2.53 (td, J = 12 and 3 Hz, 2 H), 2.24-2.10 (m, 2 H), 1.65 (bd, J = 12 Hz, 2 H), 1.42-1.26 (m, 3 H), 1.06 (qd, J = 12 and 4 Hz, 2 H).

HPLC/MS (ESI): m/z 240 (M + H); HPLC: 2.25 min.

PROCEDURE 17

4-(3,3-Difluoro-3-(4-fluorophenyl)prop-1-yl)piperidine

Step A: 1-(t-Butoxycarbonyl)-4-(hydroxymethyl)piperidine

Di-t-butyl dicarbonate (4.69 g, 21.5 mmol) was transferred in methylene chloride (9 mL) over 10 min. to a solution of 4-(hydroxymethyl)piperidine (2.47 g, 21.4 mmol) in methylene chloride (16 mL). After stirring at rt for 1 h, the solution was diluted with ether (50 mL) and washed with 2 N aq. HCl, saturated aq. sodium bicarbonate, and saturated aq. brine (25 mL of each). The organic layer was dried (sodium sulfate), decanted, and evaporated to give 4.57 g of the title compound as a crystalline solid.

^{1}H NMR (500 MHz, CD_3OD): δ 4.08 (d, J = 14 Hz, 2 H), 3.40 (d, J = 6 Hz, 2 H), 2.81-2.67 (m, 2 H), 1.71 (d, J = 13 Hz, 2 H), 1.67-1.58 (m, 1 H), 1.44 (s, 9 H), 1.09 (qd, J = 12 and 4 Hz, 2 H).

Step B: 1-(t-Butoxycarbonyl)-4-(iodomethyl)piperidine

Methanesulfonyl chloride (4.10 mL, 6.07 g, 52.9 mmol) was added dropwise to a solution of 1-(t-butoxycarbonyl)-4-(hydroxymethyl)piperidine from Step A (10.0 g, 46.4 mmol) and triethylamine (9.80 mL, 7.11 g, 70.3 mmol) in methylene chloride (140 mL) at 5-8 °C. After 1 h, the mixture was diluted with ethyl acetate (400 mL) and washed with water (200 mL). The aqueous layer was extracted with ethyl acetate (2 x 150 mL) and the combined organic layers were washed with 1 N aq. HCl (200 mL), saturated aq. sodium bicarbonate (200 mL), and saturated aq. brine (200 mL). The organic layer was dried (sodium sulfate), decanted, and evaporated to give 13.58 g of 1-(t-butoxycarbonyl)piperidin-4-yl methanesulfonate as a pale yellow solid.

A mixture of 1-(t-butoxycarbonyl)piperidin-4-yl methanesulfonate (13.58 g, 46.4 mmol) and sodium iodide (34.68 g, 232 mmol) in acetone (80 mL) was heated to reflux for 3 h. The mixture was partitioned between ether (350 mL) and water (350 mL). The organic layer was washed with saturated aq. brine (250 mL), and the aqueous layers were extracted in succession with ether (250 mL). The combined organic layers were dried (sodium sulfate), decanted, and evaporated to give the title compound (14.8 g) as a pale yellow oil.
^{1}H NMR (500 MHz, $CDCl_3$): δ 4.25-4.00 (m, 2 H), 3.12 (d, J = 4 Hz, 2 H), 2.78-2.52 (m, 2 H), 1.85 (d, J = 13 Hz, 2 H), 1.68-1.56 (m, 1 H), 1.48 (s, 9 H), 1.15 (qd, J = 12 and 4 Hz, 2 H).

Step C: ((1-(t-Butoxycarbonyl)piperidin-4-yl)methyl)triphenylphosphonium iodide

A solution of triphenylphosphine (6.63 g, 25.3 mmol) and 1-(t-butoxycarbonyl)-4-(iodomethyl)piperidine from Step B (7.96 g, 24.5 mmol) in acetonitrile (40 mL) was heated to reflux for 72 h. The solution was evaporated to give 13.35 g of white solid. A portion (12.34 g) of this material was dissolved in acetonitrile (25 mL) at 65 °C. Ethyl acetate (35 mL) was added and the mixture was allowed to cool slowly to rt and then to -20 °C. The supernatant was decanted, and the colorless crystals were washed with ethyl acetate (5 x 5 mL) and dried under vacuum to give 9.25 g of the title compound.
^{1}H NMR (500 MHz, CD_3OD): δ 7.89 (t, J = 8 Hz, 3 H), 7.86 (dd, J = 12 and 8 Hz, 6 H), 7.76 (td, J = 8 and 4 Hz, 6 H), 3.91 (bd, J = 13 Hz, 2 H), 3.44 (dd, J = 14 and 6 Hz, 2 H), 2.72-2.58 (m, 2 H), 2.08-1.96 (m, 1 H), 1.49 (bd, J = 12 Hz, 2 H), 1.41 (s, 9 H), 1.43 (qd, J = 13 and 4 Hz, 2 H).

Step D: Methyl (4-fluorobenzoyl)formate

Dimethyl oxalate (5.90 g, 50 mmol) was dissolved in THF (50 mL) and ether (50 mL) in a 3-neck round bottom flask fitted with a mechanical stirrer. The solution was stirred vigorously at -65 °C as a 1.0 M THF solution of 4-fluorophenylmagnesium bromide (60 mL, 60 mmol) was added dropwise over 40 min. The mixture was stirred 30 min at -65 °C and allowed to warm to -20 °C over 30 min before being poured into 2N aq. HCl (50 mL) with stirring. The layers were separated and the aq. layer was extracted with ether (3 x 50 mL). The combined

organic layers were washed with saturated aq. brine (2 x 50 mL), dried (sodium sulfate), decanted, and evaporated. The residue was dissolved in ethyl acetate, dried (sodium sulfate), filtered, and evaporated to give a yellow solid. The crude product was dissolved in warm hexane (25 mL), filtered, and cooled to -20 °C. Filtration followed by washing with cold hexane (15 mL) gave 4.95 g of the title compound as light tan crystals.
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.11 (dd, J = 9 and 5, Hz, 2 H), 7.21 (t, J = 9 Hz, 2 H), 4.00 (s, 3 H).

Step E: Methyl difluoro(4-fluorophenyl)acetate

Methyl (4-fluorobenzoyl)formate from Step D(4.75 g, 26.1 mmol) was added to (diethylamino)sulfur trifluoride (7.0 mL, 8.5 g, 53 mmol). The mixture was stirred rapidly and an ice bath was used briefly to reduce the temperature to 15 °C. After the ice bath was removed, the reaction temperature rose to 48 °C over 10 min and then slowly returned to rt. After a total of 2.75 h, the solution was carefully poured onto crushed ice (30 g) and the mixture was extracted with methylene chloride (2 x 25 mL). The organic layers were washed in succession with saturated aq. sodium bicarbonate (2 x 25 mL) and saturated aq. brine (10 mL), combined, dried (sodium sulfate) decanted, and evaporated. The residue was distilled to give the title compound as 4.16 g of light yellow liquid, B.P. 46-48 °C (0.5 mm Hg).
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63 (dd, J = 9, 5 Hz, 2 H), 7.16 (d, J = 9 Hz, 2 H), 3.88 (s, 3 H).

Step F: 1-(t-Butoxycarbonyl)-4-(3,3-difluoro-3-(4-fluorophenyl)prop-1-en-1-yl)piperidine

A solution of methyl difluoro(4-fluorophenyl)acetate (2.04 g, 10.0 mmol) from Step E in methanol (10.0 mL) was cooled to -60 °C. Sodium borohydride (380 mg, 10.0 mmol) was added in 5 portions at 10 to 15 min. intervals. The mixture was cooled to -60 to -55 °C prior to each addition and allowed to warm to -45 °C following each addition. After the last addition, the mixture was stirred 1.25 h at -50 to -45 °C. The mixture was cooled to -60 °C and quenched with 1 N aq. HCl (30 mL), with the temperature rising to -20 °C near the end of the addition. After warming to 0 °C, the mixture was extracted with ether (3 x 20 mL). The combined ether layers were washed with water (2 x 20 mL), dried (sodium sulfate), decanted,

and evaporated to give 1.95 g of crude 2,2-difluoro-2-(4-fluorophenyl)-1-methoxyethanol as a pale yellow oil.

A suspension of ((1-(t-butoxycarbonyl)piperidin-4-yl)methyl)triphenylphosphonium iodide (500 mg, 0,92 mmol) from Step C in THF (7.2 mL) was stirred at rt for 30 min. A 0.5 M toluene solution of potassium bis(trimethylsilyl)amide (1.8 mL, 0.90 mmol) was added over 3 min., giving an orange suspension. After 30 min., crude 2,2-difluoro-2-(4-fluorophenyl)-1-methoxyethanol (95 mg, 0.46 mmol) was added in THF (1.0 mL). After an additional 30 min, the mixture was quenched by the addition of saturated aq. NH_4Cl (2 mL). The mixture was partitioned between ethyl acetate (50 mL) and water (75 mL), and the aqueous layer was extracted with ethyl acetate (50 mL). The organic layers were washed in succession with saturated aq. brine (25 mL), dried (sodium sulfate), decanted, and evaporated. The crude product was purified by FC, eluting with 10% ether in hexane to give 117 mg of the title compound as a 95:5 mixture of cis and trans isomers, respectively.

^1H NMR (500 MHz, $CDCl_3$): δ 7.55 (dd, J = 9 and 5 Hz, 2 H), 7.13 (t, J = 9 Hz, 2 H), 5.76 (q, J = 12 Hz, 1 H), 5.64 (dd, J = 12 and 10 Hz, 1 H), 4.20-3.95 (m, 2 H), 2.80-2.54 (m, 3 H), 1.54 (bd, J = 12 Hz, 2 H), 1.47 (s, 9 H), 1.26 (qd, J = 12 and 4 Hz, 2 H).

Step G: 1-(t-Butoxycarbonyl)-4-(3,3-difluoro-3-(4-fluorophenyl)propyl)piperidine

Potassium azodicarboxylate (695 mg, 3.58 mmol) was added to a solution of 1-(t-butoxycarbonyl)-4-(3,3-difluoro-3-(4-fluorophenyl)prop-1-en-1-yl)piperidine from Step F (424 mg, 1.19 mmol) in methanol (3.3 mL). The mixture was stirred at rt as a 9.0 M solution of acetic acid in methanol (0.80 mL, 7.2 mmol) was added over 3 h using a syringe pump. After 30 min., a second portion of potassium azodicarboxylate (695 mg, 3.58 mmol) was added followed by the addition of 9.0 M acetic acid in methanol (0.80 mL, 7.2 mmol) over 3 h. After 20 min, a third portion of potassium azodicarboxylate (695 mg, 3.58 mmol) was added followed by the addition of 9.0 M acetic acid in methanol (0.80 mL, 7.2 mmol) over 3 h. After stirring for 20 h at rt, the mixture was diluted with ethyl acetate (80 mL), and washed with 2 N aq. HCl (40 mL), saturated aq. sodium bicarbonate (40 mL), and saturated aq. brine (40 mL). The organic layer was dried (sodium sulfate), decanted, and

evaporated to give 417 mg of a mixture containing the title compound and 20-25% of unreduced 1-(t-butoxycarbonyl)-4-(3,3-difluoro-3-(4-fluorophenyl)prop-1-en-1-yl)piperidine.

A portion (365 mg) of the crude mixture containing residual olefin was hydrogenated at atmospheric pressure for 16 h using iridium black (30 mg) in a mixture of t-butanol (24 mL) and ethyl acetate (2.4 mL). The mixture was filtered, the catalyst was washed with methanol, and the filtrate was evaporated to give 371 mg of the title compound as a pale yellow syrup. R_f: 0.2 (5% ethyl acetate in hexane). ^1H NMR (500 MHz, $CDCl_3$): δ 7.46 (dd, J = 9 and 5 Hz, 2 H), 7.12 (t, J = 9 Hz, 2 H), 4.18-4.00 (m, 2 H), 2.73-2.61 (m, 2 H), 2.14 (tm, J = 16 Hz, 2 H), 1.64 (bd, J = 12 Hz, 2 H), 1.46 (s, 9 H), 1.46-1.33 (m, 3 H), 1.08 (qd, J = 12 and 4 Hz, 2 H).

Step H: 4-(3,3-Difluoro-3-(4-fluorophenyl)prop-1-yl)piperidine

1-(t-Butoxycarbonyl)-4-(3,3-difluoro-3-(4-fluorophenyl)prop-1-yl)piperidine from Step G (122 mg, 0.34 mmol) was dried by evaporation of a toluene solution at reduced pressure. The residue was dissolved in chloroform (7.6 mL) and iodotrimethylsilane (0.100 mL, 141 mg, 0.70 mmol) was added. After stirring 30 min at rt, the solution was poured into a mixture of saturated aqueous sodium bicarbonate (15 mL) and 2.5 N aq. NaOH (5 mL), and extracted with ether (50 mL). The organic layer was washed with saturated aq. brine (15 mL), dried (sodium sulfate), decanted, and evaporated to give the title compound as 88 mg of colorless oil. ^1H NMR (500 MHz, CD_3OD): δ 7.51 (dd, J = 9 and 5 Hz, 2 H), 7.17 (t, J = 9 Hz, 2 H), 2.98 (dm, J = 12 Hz, 2 H), 2.52 (td, J = 12, 3 Hz, 2 H), 2.17 (tm, J = 16 Hz, 2 H), 1.65 (bd, J = 13 Hz, 2 H), 1.42-1.26 (m, 3 H), 1.07 (qd, J = 12 and 4 Hz, 2 H). HPLC/MS (ESI): m/z 258 (M + H); HPLC: 2.64 min.

PROCEDURE 18

4-(2-((4-Fluorophenyl)sulfonyl)eth-1-yl)piperidine trifluoroacetic acid salt

Step A: 4-(2-Hydroxyeth-1-yl)piperidine acetic acid salt

Combined 4-(2-hydroxyeth-1-yl)pyridine (25 g, 0.2 mol) and platinum oxide (1 g, 4.4 mmol) in 400 mL acetic acid. Placed under 45 psi hydrogen at 60 °C for 24 h. Decanted, then filtered through Celite and removed the solvent to afford 38 g (100%) of the crude product, which was used without further purification.

Step B: 4-(2-Hydroxyeth-1-yl)-1-tert-butoxycarbonylpiperidine

Dissolved sodium bicarbonate (134 g, 1.6 mol) and 4-(2-hydroxyeth-1-yl)piperidine acetic acid salt (38 g, 0.2 mol, from Step A) in 500 mL of 50% tetrahydrofuran in water. Added di-tert-butyl dicarbonate (35 g, 0.2 mol) and stirred at rt overnight. Diluted with ethyl acetate and extracted the aq. layer with 2 x 300 mL of ethyl acetate. Washed the combined organic layers with 2 x 300 mL of 1 N HCl and brine. Dried over magnesium sulfate and concentrated to afford 37.4 g (81%) of the title compound.

ESI-MS: 230 (M+H); HPLC A: 2.76 min.

Step C: 4-(2-Iodoeth-1-yl)-1-tert-butoxycarbonylpiperidine

Combined 4-(2-hydroxyeth-1-yl)-1-tert-butoxylcarbonylpiperidine (37.4 g, 0.16 mol, from Step B), triphenylphosphine (55 g, 0.21 mol) and imidazole (14 g, 0.21 mol) in 800 mL of 33% acetonitrile in ether. Cooled to 0 °C and added iodine (56 g, 0.22 mol) portionwise. The iodine is de-colored until the endpoint of the reaction. Diluted with 1 L of ether. Washed organic layer with 2 x 500 mL each of sat'd. aq. $Na_2S_2O_3$, sat. aq. $CuSO_4$ and brine. Dried over magnesium sulfate, filtered and concentrated. Triphenylphosphine oxide precipitates. Added ether and filtered the slurry through a plug of silica gel. Purified a portion of the crude material by flash chromatography (5 % ethyl acetate in hexane eluent) to afford the title compound. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.10 (br s, 2 H), 3.23 (t, 2 H, J = 7.2 Hz), 2.72 (br t, 2 H, 12.3 Hz), 1.79 (q, 2 H, J = 7 Hz), 1.67 (br d, 2 H, 14 Hz), 1.61 (m, 1 H), 1.47 (s, 9 H), 1.14 (qd, 2 H, J = 4.3, 12 Hz); ESI-MS: 340 (M+H); HPLC A: 3.74 min.

Step D: 4-(2-(4-Fluorophenylthio)eth-1-yl)-1-tert-butoxycarbonylpiperidine

To a slurry of sodium hydride (47 mg, 60% in mineral oil, 1.2 mmol) in tetrahydrofuran at 0 °C was added 4-fluorothiophenol (0.1 mL, 0.94 mmol). The reaction mixture was warmed to rt. for 20 min, followed by addition of 4-(2-iodoeth-1-yl)-1-tert-butoxycarbonylpiperidine (265 mg, 0.78 mmol, from Step C). The reaction was then heated to reflux for 10 min, cooled and diluted with ether. The organic layer was washed with 1 N NaOH, dried over magnesium sulfate and concentrated to provide 252 mg (95%) of the title compound. ESI-MS: 340.0 (M+H); HPLC A: 4.07 min.

Step E: 4-(2-(4-Fluorophenylsulfonyl)eth-1-yl)piperidine trifluoroacetic acid salt

Added a solution of oxone (1.14 g, 1.86 mmol) in water to a solution of 4-(2-(4-fluorophenylthio)eth-1-yl)-1-tert-butoxycarbonylpiperidine (252 mg, 0.74 mmol, from Step D) in methanol at 0 °C. Warmed to rt. After 90 min., added an additional 0.5g of oxone. After 3 h, the reaction mixture was diluted with methylene chloride and washed with 1 N NaOH containing sodium bisulfite. The aq. layer was extracted twice with methylene chloride, and the combined organic layers were dried over magnesium sulfate. The solution was concentrated and dissolved in 5% trifluoroacetic acid in methylene chloride for 1 h. The solvent was evaporated to afford 297 mg (100%) of the title compound.
ESI-MS: 239.8 (M+H); HPLC A: 2.54 min.

PROCEDURE 19

4-((5-Benzyl)pyrid-3-yl)piperidine di-TFA salt

Step A: N-tert-Butoxycarbonyl-1,2,5,6-tetrahydropyridine-4-trifluoromethane sulfonate.

A dry flask under nitrogen was charged with a solution of sodium hexamethyldisilazide (11 mL, 1.0 M in THF) and was cooled to –78 °C. A solution of N-tert-butoxycarbonyl-4-piperidone (2.0 g, 10 mmol) in 10 mL THF was added dropwise via cannula. After 30 min. a solution of 2-(N,N-bis(trifluoromethanesulfonyl) amino-5-chloropyridine (4.7 g, 12 mmol) in 15 mL THF was added. The mixture was warmed to room temperature, quenched with sat'd ammonium chloride and extracted with ethyl acetate. The ethyl acetate layer was separated and washed with sat'd brine then dried over sodium sulfate and concentrated. Flash chromatography (100 g silica, 10/1 Hexane/ethyl acetate) afforded 1.9 g (58 %) of the title compound.
^{1}H NMR (400 MHz, $CDCl_3$). δ 1.5 (s, 9H), 2.4-2.48 (m, 2H), 3.62-3.68 (t, 2H), 4.05-4.07 (m, 2H), 5.77-5.8 (bs, 1H).

Step B: N-tert-Butoxycarbonyl-4-trimethylstannyl-1,2,5,6-tetrahydropyridine

A dry flask under nitrogen was charged with 20 mL THF, lithium chloride (1.6 g, 37.3 mmol), tetrakistriphenylphosphine palladium(0), (331 mg, 0.28 mmol) and hexamethyldistannane (1.2 mL, 5.7 mmol). N-tert-butoxycarbonyl-1,2,5,6-tetrahydropyridine-4-trifluoromethane sulfonate (1.9 g, 5.7 mmol) was added and the mixture was stirred overnight at 60 °C. The mixture was diluted with water and extracted with ethyl acetate (3x150 mL). The combined organic layers were dried over sodium sulfate and concentrated. Flash chromatography (100 g silica, 20/1 Hexane/ethyl acetate) afforded 1.56 g (79 %) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$). δ 0.5 (s, 9H), 1.5 (s, 9H), 2.25-2.35 (m, 2H), 3.62-3.68 (t, 2H), 3.95-3.97 (m, 2H), 5.77-5.8 (bs, 1H).

Step C: 3-Bromo-5-benzylpyridine

A dry flask under nitrogen was charged with zinc chloride (16 mL, 0.5 M in THF, 8 mmol), and a solution of phenylmagnesium chloride (4 mL, 2.0 M in THF, 8 mmol). The mixture was heated to 50 °C for 3h then cooled to room temperature and transferred via cannula to a solution of 3,5-dibromopyridine (1.26 g, 5.3 mmol), copper iodide (61 mg, 0.32 mmol), and bis(diphenylphosphino)ferrocene palladium dichloride (218 mg, 0.27 mmol) in 15 mL THF. The resulting mixture was heated to 50 °C overnight. Sat'd ammonium chloride was added and the mixture was extracted with ethyl acetate. The organic portion was dried over sodium sulfate and concentrated. Flash chromatography (8/1 hexane/ethyl acetate) afforded 433 mg (33 %) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$). δ 4.02 (s, 2H), 7.18-7.4 (m, 8H), 7.65 (s, 1H).

Step D: 4-((5-Benzyl)pyrid-3-yl)piperidine di-TFA

A flask was purged with nitrogen and charged with DMF, 3-bromo-5-benzylpyridine (618 mg, 2.5 mmol, from Step C), tetrakis triphenylphosphine palladium (58 mg, 0.05 mmol), and N-tert-butoxycarbonyl-4-trimethylstannyl-1,2,5,6-tetrahydropyridine (1.04 g, 3 mmol). The mixture was heated to 100 °C and stirred for 10 h. An additional portion of tetrakis triphenylphosphine palladium (40 mg, 0.03 mmol) was added and stirring was continued for 14 h. The solution was cooled and diluted with ethyl acetate then washed with water, dried over sodium sulfate and concentrated. Flash chromatography (2.5/1 hexane/ethyl acetate) afforded 590 mg (67 %) of the coupling product. The product was dissolved in 4 mL methanol and 50 mg

10% Pd/C was added. The mixture was stirred under 1 atm of hydrogen for 3h. The catalyst was filtered off and the residue was dissolved in 1/1 TFA/methylene chloride. Removal of the solvent and drying under vacuum afforded the title compound as its TFA salt.

^{1}H NMR (500 MHz, $CDCl_3$). δ 1.55-1.64 (m, 2H), 1.75-1.8 (d, 2H), 2.57-2.62 (m, 1H), 2.68-2.73 (t, 2H), 3.15-3.2 (d, 2H), 7.14-7.15 (d, 2H), 7.19-7.21 (m, 1H), 7.26-7.32 (m, 3H), 8.30-8.31 (d, 2H).

PROCEDURE 20

4-(2-(Benzyl)-(2H)-tetrazol-5-yl)piperidine

Step A: 1-(t-Butoxycarbonyl)-4-cyanopiperidine

Isonipecotamide (10.0 g, 78.0 mmol) was added in portions to 25 mL of $POCl_3$ at 0 °C. The cooling was removed and the mixture was allowed to reach rt. The mixture was heated at reflux for 2 h, then cooled to rt. The mixture was poured onto 100 g of ice. The pH of the aqueous mixture was adjusted to 11 with solid KOH and extracted with 4 x 200 mL of methylene chloride. The extracts were combined, dried over magnesium sulfate and concentrated to afford 8.0 g of crude (4-cyano)piperidine.

The crude (4-cyano)piperidine was dissolved in 50 mL of methanol and treated with 17.0 g (78.0 mmol) of di-t-butyl dicarbonate and the resulting mixture was stirred at rt for 1 h. The mixture was concentrated. Flash chromatography on 250 g of silica gel using 1:1 v/v hexanes/ether afforded 13.4 g (80%) of the title compound:

^{1}H NMR (300 MHz) δ 1.46 (s, 9H), 1.76-1.96 (4H), 2.78-2.82 (m, 1H), 3.31-3.37 (m, 2H), 3.63-3.69 (m, 2H).

Step B: 1-(t-Butoxycarbonyl)-4-(1H-tetrazol-5-yl)piperidine

A mixture of 2.10 g (10.0 mmol) of 1-(t-butoxycarbonyl)-4-cyanopiperidine (from Step A), 1.95 g (30.0 mmol) of sodium azide and 1.60 g (30.0 mmol) of ammonium chloride in 20 mL of DMF was stirred at 100 °C for 20 h. The mixture was cooled and partitioned between 200 mL of methylene chloride and 200 mL of 1.0 N HCl and the layers were separated. The organic layer was washed with 200 mL of water, dried over magnesium sulfate and concentrated. Flash

chromatography on 50 g of silica gel using 4:1 v/v methylene chloride/ethyl acetate + 1% acetic acid, then 2:1 v/v methylene chloride/ethyl acetate + 1% acetic acid as the eluent afforded 1.51 g (60%) of the title compound:
^{1}H NMR (500 MHz) δ 1.49 (s, 9H), 1.83-1.89 (m, 2H), 2.13-2.15 (m, 2H), 2.96-3.04 (m, 2H), 3.13-3.36 (m, 1H), 4.14-4.22 (m, 2H).

Step C: 1-(t-Butoxycarbonyl)-4-((1-benzyl)-(1H)-tetrazol-5-yl)piperidine and 1-(t-Butoxycarbonyl)-4-((2-benzyl)-(2H)-tetrazol-5-yl)piperidine

A solution of 438 mg (1.7 mmol) of 1-(t-butoxycarbonyl)-4-(1H-tetrazol-5-yl)piperidine (from Step B) in 2 mL of DMF at 0 ° C was treated with 83 mg (0.50 mmol) of sodium hydride (60% in mineral oil) and 0.41 mL (3.4 mmol) of benzyl bromide. The resulting mixture was warmed to rt and stirred for 2.5 h. The mixture was partitioned between 50 mL of ether and 50 mL of water and the layers were separated. The organic layer was washed with 50 mL sat'd brine, dried over magnesium sulfate and concentrated. Flash chromatography using 2:1 v/v methylene chloride/ether, then 1:2 v/v methylene chloride/ether afforded 85 mg (15%) of 1-(t-butoxycarbonyl)-4-(2-(benzyl)-(2H)tetrazol-5-yl)piperidine. Elution with 2:1 v/v ethyl acetate/methylene chloride afforded 95 mg (17%) of 1-(t-butoxycarbonyl)-4-(1-(benzyl)-(1H)-tetrazol-5-yl)piperidine.
For 1-(t-butoxycarbonyl)-4-(2-(benzyl)-(2H)-tetrazol-5-yl)piperidine:
^{1}H NMR (500 MHz) δ 1.47 (s, 9H), 1.76-1.84 (2H), 2.02-2.05 (2H), 2.91-2.95 (2H), 3.07-3.12 (m, 1H), 4.00-4.20 (2H), 5.71 (s, 2H), 7.35-7.40 (5H).
For 1-(t-butoxycarbonyl)-4-(1-(benzyl)-(1H)-tetrazol-5-yl)piperidine:
^{1}H NMR (500 MHz) δ 1.45 (s, 9H), 1.59-1.61 (2H), 1.76-1.84 (2H), 2.70-2.80 (2H), 2.85-2.89 (m, 1H), 4.00-4.20 (2H), 5.55 (s, 2H), 7.17-7.19 (2H), 7.36-7.39 (3H).

Step D: 4-(2-(Benzyl)-(2H)-tetrazol-5-yl)piperidine

A solution of 85 mg (0.25 mmol) of 1-(t-butoxycarbonyl)-4-((2-benzyl)tetrazol-5-yl)piperidine (from Step C) in 2 mL of 1:1 v/v methylene chloride/TFA was stirred at rt for 2 h. The solution was concentrated. Flash chromatography on silica gel using 19:1:0.1 v/v/v methylene chloride/methanol/NH_4OH as the Eluant afforded 57 mg (94%) of the title compound.

PROCEDURE 21

4-(1-(4-Methylsulfonylbenzyl)-3-ethyl-(1H)-pyrazol-4-yl)piperidine di-TFA salt

Step A: N-tert-Butoxycarbonyl-4-piperid-4-ylacetaldehyde

A solution of oxalyl chloride (2.4 mL, 27.5 mmol) in 125 mL methylene chloride was cooled to –78 °C and DMSO (3.3 mL, 47.1 mmol) was added slowly. After 10 min a solution of 2-(N-tert-butoxycarbonylpiperidin-4-yl)ethanol (4.5 g, 19.6 mmol) in 10 mL methylene chloride was added. The mixture was stirred for 20 min then triethylamine (13.6 mL, 98.1 mmol) was added and the mixture was warmed to room temperature. After 30 min the mixture was diluted with ethyl acetate and washed with water (3x). The organic portion was dried over sodium sulfate and concentrated. Flash chromatography (3/1 hexane/ethyl acetate) afforded 3.7 g (83 %) of the desired aldehyde.

^{1}H NMR (400 MHz, $CDCl_3$). δ 1.13-1.43 (m, 2H), 1.48 (s, 9H), 1.68-1.77 (m, 2H), 2.04-2.11 (m, 1H), 2.38-2.41 (d, 2H), 2.71-2.8 (m, 2H), 4.04-4.14 (m, 2H), 9.8 (s, 1H).

Step B: 3-Ethyl-4-(N-t-butoxycarbonylpiperidin-4-yl)-(1H)-pyrazole

A solution of N-tert-butoxycarbonylpiperidin-4-ylacetaldehyde (4.5 g, 19.8 mmol, from Step A), and morpholine (1.7 mL, 19.8 mmol) in 100 mL benzene was refluxed using a dean-stark apparatus. After refluxing over night the mixture was concentrated to provide the enamine. The crude enamine was dissolved in 40 mL methylene chloride and the solution was cooled to 10 °C. Propionyl chloride (1.7 mL, 19.8 mmol) and then triethylamine (1.4 mL, 9.9 mmol) were added. The mixture was gradually warmed to room temperature and stirred for 40 h then concentrated. The residue was dissolved in 60 mL of ethanol and hydrazine (6.2 mL, 198 mmol) was added. The solution was refluxed for 5 h. The solvent was removed and ethyl acetate was added. The organic was washed with water and sat'd sodium chloride then dried over magnesium sulfate and concentrated. Flash chromatography (0.5% methanol/methylene chloride -> 2 % methanol/methylene chloride) afforded 2.1 g (38 %) of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$). δ 1.25-1.31 (t, 3H), 1.44-1.57 (m, 1H), 1.46 (s, 9H), 1.78-1.83 (s, 2H), 2.53-2.6 (m, 1H), 2.62-2.7 (q, 2H), 2.77-2.82 (m, 2H), 4.12-4.23 (m, 2H), 7.32 (s, 1H).

Step C: 4-(1-(4-Methylsulfonylbenzyl)-3-ethyl-(1H)-pyrazol-4-yl)-N-t-butoxylcarbonylpiperidine

A dry flask was charged with 5 mL DMF and sodium hydride (224 mg, 60 % dispersion in mineral oil, 5.6 mmol). A solution of 3-ethyl-4-(N-t-butoxycarbonylpiperidin-4-yl)-(1H)-pyrazole (1.3 g, 4.7 mmol, from Step B) in 5 mL DMF was added. The mixture was stirred for 1h at room temperature and a solution of (4-methylsulfonyl)benzyl chloride (1.05 g, 5.2 mmol) in 5 mL DMF was added. After 3 h the solvent was removed and the product was purified by preparative HPLC (35% acetonitrile/water -> 85 % acetonitrile/water, C-18 stationary phase) to give 0.5 g of product as a mixture of isomeric N-alkylation products. The isomers were separated by preparative HPLC using a chiral stationary phase (Chiracel-OJ, 1/1 hexane/ethanol) to provide 210 mg (10 %) of the desired isomer along with 70 mg (3%) of the undesired isomer. The substitution pattern of both isomers was determined by NOE difference.

^{1}H NMR (400 MHz, $CDCl_3$, desired isomer). δ 1.25-1.31 (t, 3H), 1.38-1.47 (m, 1H), 1.46 (s, 9H), 1.8-1.85 (m, 2H), 2.5-2.6 (m, 1H), 2.6-2.66 (q, 2H), 2.75-2.82 (m, 2H), 3.03 (s, 3H), 4.13-4.22 (m, 2H), 5.32 (s, 2H), 7.13 (s, 1H), 7.28-7.31 (d, 2H), 7.89-7.91 (d, 2H).

Step D: 4-(1-(4-Methylsulfonylbenzyl)-3-ethyl-(1H)-pyrazol-4-yl)piperidine di-TFA salt

4-((1-(4-Methylsulfonylbenzyl)-3-ethyl)-(1H)-pyrazol-4-yl)-N-t-butoxylcarbonylpiperidine from Step C was treated with TFA for 1 h and evaporated to afford the title compound as the TFA salt.

PROCEDURE 22

4-(2-Benzylthiazol-5-yl)piperidine di-HCl salt (Method A)

Step A: 1-t-Butyloxycarbonyl-4-(nitromethylcarbonyl) piperidine

To a solution of 1-t-butyloxycarbonylpiperidine-4-carboxylic acid (22.9 g, 100 mmol) in 200 mL of anhydrous THF was added carbonyl diimidazole (20.0 g, 125 mmol) under nitrogen. Effervescence was observed and the reaction mixture was stirred 1 h at ambient temperature. Freshly distilled nitromethane (7.4 mL, 135 mmol) followed by DBU (21.0 mL, 140 mmol) were added. The resulting reaction mixture was stirred for 1 day at room temperature. After dilution with ethyl

acetate, the mixture was washed with 2N HCl and brine. The organic phase was dried over anhydrous magnesium sulfate. Evaporation of the solvent followed by the purification of the residue on silica gel using 1:1 mixture of ethyl acetate -hexane with 1% acetic acid as an eluent gave 25 g of the nitroketone as a semi solid. After removal of last traces of acetic acid by azeotroping with toluene.

^{1}H NMR ($CDCl_3$): δ 1.48(9H,s); 1.65,1.90,2.65,2.80,4.15 (all multiplets); 5.36(2H,s).

Step B: 1-t-Butyloxycarbonyl-4-(1-hydroxy-2-nitro)ethyl)piperidine

Sodium borohydride (1.52 g, 40 mmol) was added portionwise to a suspension of 1-t-butyloxycarbonyl-4-(nitromethylcarbonyl) piperidine (10.5 g, 40 mmol) from Step A in methanol (80 mL) at 0 °C. After 6.5 h, the solvent was removed *in vacuo*. The residue was diluted with ethyl acetate and stirred with 2N HCl and the layers were separated. The organic phase was washed with brine and dried over magnesium sulfate. Solvent removal gave 9.1 g of the desired product as amorphous solid.

^{1}H NMR ($CDCl_3$): δ 1.45(9H,s); 4.45(2H, m); 1.3,1.65,1.85,2.7,4.2 (multiplets)

Step C: 1-t-Butyloxycarbonyl-4-(1-hydroxy-2-amino)ethylpiperidine

To a stirred suspension of 1-t-butyloxycarbonyl-4-(1-hydroxy-2-nitro)ethyl)piperidine (9.0 g, 33 mmol) from Step B in anhydrous methanol (100 mL),10% Pd-C (2.0 g) followed by ammonium formate (12.6 g, 200 mmol) were cautiously added. The reaction mixture was stirred 1.5 days at ambient temperature. The catalyst was filtered through a pad of celite and washed with methanol. The filtrate was concentrated after adding 42 mL of triethylamine to free the product from any formic acid salts. The residue was purified on silica gel using 10:10:1 mixture of ethyl acetate, hexane and NH_4OH as solvent to yield 6.9 g of the desired amino alcohol as white solid after azeotroping with toluene.

^{1}H NMR ($CDCl_3$): δ 1.5(9H,s); 3.6(2H,s)1.2,1.75,2.6,3.24,3.4,4.15 (all multiplets).

Step D: 1-t-Butyloxycarbonyl-4-(1-hydroxy-2-phenylacetylamino)ethylpiperidine

Phenylacetyl chloride (0.44 mL, 3.3 mmol) was added dropwise to a mixture of 1-t-butyloxycarbonyl-4-(1-hydroxy-2-amino)ethylpiperidine (0.732 g, 3

mmol) from Step C and triethylamine (0,465 mL, 3.3 mmol) in methylene chloride (15 mL) at ice bath temperature and the bath was removed. After stirring for 3 h at room temperature, the reaction mixture was diluted with ethyl acetate and washed with saturated sodium bicarbonate and brine. The organic phase was dried over anhydrous magnesium sulfate. Solvent removal gave a crude product which was used in the next step without further purification.
^{1}H NMR ($CDCl_3$): δ 1.45(9H,s); 3.42(2H,s); 1.2,1.75,2.6,3.2,3.42,4.12 (all multiplets).

Step E: 1-t-Butyloxycarbonyl-4-(2-phenylacetamido)acetylpiperidine
To a stirred solution of 1-t-butyloxycarbonyl-4-(1-hydroxy-2-phenylacetylamino)ethylpiperidine from Step D in acetone at ice bath temperature 8 N Jones reagent was added until the orange color of the reagent persisted. After stirring for 0.5 h, 0.2 mL of isopropanol was added and the stirring was continued for 0.5 h. Solvent was removed *in vacuo* and the residue was partitioned between water and ethyl acetate. The organic phase was washed with brine and dried over anhydrous magnesium sulfate. Solvent removal gave an oil which was purified on silica gel using 1: ethyl acetate -hexane as solvent to yield 606 mg of the desired ketone as oil.
^{1}H NMR ($CDCl_3$): δ 1.46(9H,s); 3.62(2H,s); 4.18(2H,d, J=2); 1.45,1.8,2.5,2.78,4.1, 7.35,7.4 (all multiplets)

Step F: 1-t-Butyloxycarbonyl-4-(2-benzylthiazol-5-yl)piperidine
A mixture of 1-t-butyloxycarbonyl-4-(2-phenylacetamido)acetylpiperidine (595 mg, 1.653 mmol) from Step E and Lawesson's reagent (607 mg, 1.66 mmol) in 5 mL of toluene was heated to 120 °C for 3.5 h. After cooling, 3:1 mixture of ethyl acetate and methylene chloride and saturated sodium bicarbonate solution were added and the mixture was stirred for 0.5 h. The organic phase was separated and washed with brine. Solvent removal gave a crude product which was purified on silica gel using 2:3 mixture of ethyl acetate -hexane as solvent to give 330 mg of the desired product.
^{1}H NMR ($CDCl_3$): δ 1.45(9H,s); 4.4(2H,s); 7.46(1H.s); 1.58,1.95,2.85,2.95,4.2 (all multiplets).

Step G: 4-(2-Benzylthiazol-5-yl)piperidine di-hydrochloride

Acetyl chloride (0.3 mL) was added dropwise to a solution 1-t-butyloxycarbonyl-4-(2-benzylthiazol-5-yl)piperidine from Step F in methanol (2 mL) at ice bath temperature. The reaction mixture was stirred 3.5 h as it warmed to room temperature. Solvent removal *in vacuo* gave the desire amine as glassy solid.
^{1}H NMR ($CDCl_3$): δ 4.58(2H,s); 8.02(1H,s); 1.94,2.24.3.15,3.35,3.45 (all multiplets)

PROCEDURE 23

4-(2-Benzylthiazol-5-yl)piperidine di-HCl salt (Method B)

Step A: 1-t-Butyloxycarbonyl-4-(2-hydroxyethyl)piperidine

A mixture of 4-(2-hydroxyethyl) piperidine (5.0 g, 40 mmol), di-t-butyl dicarbonate (10.9 g, 50 mmol), and triethylamine (7 mL, 50 mmol) in 100 mL of anhydrous methylene chloride was stirred overnight at room temperature. Volatiles were removed *in vacuo* and the resulting oil was purified on a silica gel column using 20% ethyl acetate in hexane as eluent to give 7.9 g of the desired product as a colorless oil.

Step B: 1-t-Butyloxycarbonyl-4-formylylmethylpiperidine

Oxalyl chloride (2.2 mL, 25 mmol) was added to 75 mL of anhydrous methylene chloride at -78^{0}C. DMSO (3.5 mL, 50 mmol) was then added dropwise over 5 min, and the resulting mixture was stirred for 15 min. 1-t-Butyloxycarbonyl-4-(2-hydroxyethyl)piperidine (2.29 g, 10 mmol, Step A) was dissolved in 5 mL of anhydrous methylene chloride and added over 10 min to the above mixture. After stirring 30 min, DIEA (17.4 mL, 100 mmol) was added over 10 min. The mixture was then warmed to 0 ^{0}C and maintained at that temperature for 1 h. After quenching with water, the reaction mixture was diluted with 75 mL of methylene chloride and the layers were separated. The organic phase was washed with 3 x 50 mL of water and dried over anhydrous magnesium sulfate. Solvent removal gave an oil, which was purified on silica gel using 20% ethyl acetate in hexane to give 2.05 g of the desired aldehyde which hardened overnight into an oily solid.
NMR: ($CDCl_3$): δ 2.15 (2H, d, J=3); 9.8 (1H,s); 1.2, 1.5, 1.7, 2.75, 4.1(all multiplets)

Step C: 1-t-Butyloxycarbonyl-4-(□-bromo-formylmethyl)piperidine

A mixture of 1-t-butyloxycarbonyl-4-formylylmethylpiperidine (0.57 g, 2.25 mmol, step B), 3,3-dibromo-Meldrum's acid (0.75 g, 2.5 mmol) in 10 mL of anhydrous ether was stirred for 2 days at room temperature under nitrogen. The reaction mixture was diluted with ethyl acetate and washed with sat'd. sodium bicarbonate solution. The organic phase was dried over anhydrous magnesium sulfate. Solvent removal and purification on silica gel using 20% ethyl acetate in hexane as solvent gave 59% of the pure bromo aldehyde as a colorless oil.
^{1}H NMR: ($CDCl_3$): δ: 4.04 (1H,dd; J=1.5;2); 9.46 (1H,d; J=1.5) 1.35, 1.7, 1.95, 2.1, 2.75, 4.2 (all multiplets)

Step D: 1-t-Butyloxycarbonyl-4-(2-benzylthiazol-5-yl)piperidine

A mixture of 1-t-butyloxycarbonyl-4-(α-bromo-formylmethyl)piperidine (612 mg, 2 mmol), benzyl thioamide (500 mg, 2.55 mmol) in 10 mL of anhydrous toluene was heated to reflux for 6 h. Solvent was then removed and the residue was purified on silica gel using 25% ethyl acetate in hexane as solvent to give 350 mg of the desired thiazole as an oil.
^{1}H NMR ($CDCl_3$): δ 1.45(9H,s); 4.4(2H,s); 7.46(1H.s); 1.58,1.95,2.85,2.95,4.2 (all multiplets).

Step E: 4-(2-Benzylthiazol-5-yl)piperidine di-hydrochloride

The title compound was prepared by removal of the protecting group of 1-t-butyloxycarbonyl-4-(2-benzylthiazol-5-yl)piperidine as described in Example 22, Step G.

PROCEDURE 24

4-(2-Benzyl-4-methylthiazol-5-yl)piperidine

The title thiazole was prepared according to the method of Procedure 22 by substituting nitroethane for nitromethane in Step A.

PROCEDURE 25

4-(2-Benzyl-4-ethylthiazol-5-yl)piperidine

The title compound was obtained by the procedure of Procedure 22 by substituting nitropropane for nitromethane in Step A.

PROCEDURE 26

4-(2-(2-Pyridylmethyl)thiazol-5-yl)piperidine di-HCl salt

Step A: 1-t-Butyloxycarbonyl-4-((1-hydroxy)-2-(2-pyridylmethyl)carbonylamino)ethylpiperidine

To 0.361 g (2.08 mmol) of 2-pyridyleacetic acid hydrochloride in 8 mL of methylene chloride, 0.337 g (2.5 mmol) of 1-hydroxybenzotriazole, 0.478 g (2.5 mmol) of EDC and 0.57 mL (5.2 mmol) of N-methylmorpholine were added. After 10 min 0.508 g (2.08 mmol) of 1-t-butyloxycarbonyl-4-(2-amino-1-hydroxy)ethylpiperidine from Procedure 22, Step C was added and the solution was stirred overnight. The reaction was quenched with saturated sodium bicarbonate and extracted with methylene chloride. The combined methylene chloride layer was washed with brine, dried and concentrated. The residue was chromatographed on a flash column using a gradient of 5-10% methanol in ethyl acetate containing 1% triethylamine to isolate 0.68 g of the desired product.

^{1}H NMR ($CDCl_3$): δ 1.24 (m, 3H), 1.45 (s, 9H), 1.58 (m, 1H), 1.82 (m, 1H), 2.6 (br, 2H), 3.21 (m, 1H), 3.49 (m, 2H), 3.75 (s, 2H), 4.12 (br, 2H), 7.22 (m, 1H), 7..29 (d, 1H), 7.69 (m, 1H), 852 (m, 1H).

Step B: 1-t-Butyloxycarbonyl-4-(2-(2-pyridylmethyl)carbonylamino)acetylpiperidine

To a solution of 0.22 mL (3.2 mmol) of DMSO in 1 mL of methylene chloride cooled in a dry ice-acetone bath, 0.14 mL (1.6 mmol) of oxalyl chloride was added. After 0.5 h, 0.145 g of 1-t-butyloxycarbonyl-4-((1-hydroxy)-2-(2-pyridylmethyl)carbonylamino)ethylpiperidine (Step A) in 1 mL of methylene chloride was added. After 1 h, 0.89 mL (6.38 mmol) of triethylamine was added, the cold bath was removed and the reaction was stirred for 1.5 h. The solution was partitioned between water and methylene chloride. The organic layer was washed with brine, dried and concentrated. The residue was purified on a prep TLC plate using 5% methanol - ethyl acetate as an eluent to furnish 67 mg of the desired product.

^{1}H NMR ($CDCl_3$): δ 1.45 (s, 9H),1.5-2.0 (m, 4H), 2.53 9m, 1H), 2.77 (br, 2H), 3.79 (s, 2H), 4.1 (br, 2H), 4.22 (d, 2H), 7.2-8.0 (m, 3H), 8.61 (d, 1H).

Step C: 1-t-Butyloxycarbonyl-4-(2-(2-pyridylmethyl)thiazol-5-yl)piperidine

The title compound was prepared by reacting 1-t-butyloxycarbonyl-4-(2-(2-pyridylmethyl)carbonylamino)acetylpiperidine (Step B) with Lawesson's reagent as described in Procedure 22, Step F.

^{1}H NMR ($CDCl_3$): δ 1.47 (s, 9H), 1.6 (m, 2H), 1.99 (m, 2H), 2.82 (br, 2H), 2.94 (m, 1H), 4.17 (br, 2H), 4.48 (s, 2H), 7.2-7.8 (m, 4H), 8.6 (br, 1H).

Step D: 4-(2-(2-Pyridylmethyl)thiazole-5-yl)piperidine di-HCl salt

Removal of the t-butyloxycarbonyl protecting group as described in Procedure 22, Step G furnished the title compound.

PROCEDURE 27

4-(Imidazo[1,2-a]pyridin-3-yl)piperidine di-TFA salt

Step A: 1-(t-Butoxycarbonyl)-4-(imidazo[1,2-a]pyridin-3-yl)piperidine

To a solution of 1.15 g of 1-(t-butoxycarbonyl)-4-(1-bromo-2-oxoethyl)piperidine (from Procedure 23, Step C) in 15 mL ethanol was added 388 mg of 2-aminopyridine. After refluxing for 18 h, the solvent was evaporated. The mixture was partitioned between ethyl acetate and saturated sodium bicarbonate solution. Aqueous layer was extracted with ethyl acetate (3x). The combined organic phase was washed with brine, dried over magnesium sulfate and concentrated. The residue was purified by flash chromatography with 50% ethyl acetate in hexanes, followed by 100% ethyl acetate to give 401 mg of the title compound as a solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.48 (s, 9H), 1.70 (m, 2H), 2.06 (d, J = 13Hz, 2H), 2.93-3.02 (m, 3H), 4.26 (br, 2H), 6.87 (t, J = 6.8 Hz, 1H). 7.21(m, 1H), 7.44(s, 1H), 7. 69(d, J= 9.2 Hz,1H), 7.99 (d, J = 6.9 Hz, 1H).

Step B: 4-Imidazo[1,2-a]pyridin-3-yl)piperidine di-TFA salt

To 100 mg of 1-(t-butoxycarbonyl)-4-(imidazo[1,2-a]pyridin-3-yl)piperidine from Step A was added 2 mL TFA. The reaction was stirred at rt for 1 h. The mixture was concentrated under reduced pressure to afford 180 mg of a viscous oil.

PROCEDURE 28

4-(7-*t*-Butylimidazo[1,2-a]pyridin-3-yl)piperidine, TFA salt

Step A: 2-Amino-4-t-butylpyridine

To 790 mg of sodium amide were added 20 mL of *N,N*-dimethylaniline and 2.74 g of 4-*t*-butyl pyridine at rt. The mixture was stirred at 150 °C for 6 h. During this period, 3 more portions of sodium amide (790 mg each) were added. The reaction was cooled down to rt. The mixture was partitioned between ethyl acetate and water. Aqueous layer was extracted with ethyl acetate (3x). The combined organic phase was washed with brine, dried over magnesium sulfate and concentrated. The residue was purified by flash chromatography with 50% ethyl acetate in hexanes followed by 100% ethyl acetate to give 1.68 g of the title compound as a solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.21 (s, 9H), 6.44 (t, 1H), 6.6.62 (dd, J= 5.5 Hz and, 1H), 7.94 (d, J = 5.5Hz, 1H).

Step B: 1-(t-Butoxycarbonyl)-4-(7-t-butylimidazo[1,2-a]pyridin-3-yl)piperidine

The title compound was prepared from 470 mg of 1-(t-butoxycarbonyl)-4-(1-bromo-2-oxoethyl)piperidine (from Procedure 23, Step C) and 277 mg of 2-amino-4-*t*-butyl pyridine (from Step A) in 12 mL ethanol using a procedure analogous to that described in Example 235 , Step A to provide 130 mg of the title compound as a solid.

Step C: 4-(7-t-Butylimidazo[1,2-a]pyridin-3-yl)piperidine, TFA salt

The title compound was prepared from 35 mg of 1-(t-butoxycarbonyl)-4-((7-t-butyl)imidazo[1,2-a]pyridin-3-yl)piperidine (from Step B) in 2 mL of TFA, using a procedure analogous to that described in Procedure 27, Step B to provide 60 mg of the title compound as a viscous oil.

PROCEDURE 29

4-(2-Ethyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-3-yl)piperidine, acetic acid salt

Step A: 2-Ethyl-imidazo[1,2-a]pyridine

The title compound was prepared from 2-aminopyridine and 1-bromo-2-butanone, employing procedures analogous to those described inProcedure 27Step A.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.34 (t, J = 7.3 Hz, 3H), 2.82 (q, J = 7.6 Hz, 2H), 6.70 (t, J = 6.6 Hz, 1H), 7.10 (m, 1H), 7.32 (s, 3H), 7.51 (d, J = 8.9 Hz, 1H), 8.03 (dd, J = 6.6, 0.9 Hz, 1H).

Step B: 3-Bromo-2-ethyl-imidazo[1,2-a]pyridine

To a solution of 2-ethyl-imidazo[1,2-a]pyridine (2.17 g, 14.9 mmol) in ethanol (25 mL) was added bromine (2.0 g, 12.5 mmol) in water (5 mL) dropwise at rt. After stirring at rt for 4h, ethanol was evaporated under reduced pressure. The residue was basified with aqueous sodium bicarbonate and extracted with methylene chloride (3X). The organic phase was washed with brine and dried over anhydrous magnesium sulfate. Concentration followed by flash chromatography eluting with 20 % ethyl acetate in hexanes, followed by 50 % ethyl acetate in hexanes afforded the title compound (1.88 g) as a viscous oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.36 (t, J = 7.5 Hz, 3H), 2.83 (q, J = 7.6 Hz, 2H), 6.88 (t, J = 6.8 Hz, 1H), 7.20 (m, 1H), 7.55 (dd, J = 8.9, 0.9 Hz, 1H), 8.05 (dd, J = 6.9, 1.2 Hz, 1H).

Step C: 2-Ethyl-3-(4-pyridyl)-imidazo[1,2-a]pyridine

To a solution of 3-bromo-2-ethyl-imidazo[1,2-a]pyridine (1.4 g, 6.28 mmol), 4-tributylstannylpyridine (2.31 g, 6.28 mmol) and Pd (II) $(Ph_3P)_2Cl_2$ (442 mg, 0.63 mmol) in toluene (5 mL) was added lithium chloride (26.7 mg, 0.63). After refluxing for 18 h, the mixture was partitioned between ethyl acetate and aqueous sodium bicarbonate. The aqueous layer was extracted with ethyl acetate (3X). Combined organic phase was washed with brine and dried over anhydrous magnesium sulfate. Concentration followed by flash chromatography eluting with 100 % ethyl acetate, then 10 % methanol in methylene chloride afforded the title compound (543 mg) as a viscous oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.36 (t, J = 7.5 Hz, 3H), 2.84 (q, J = 7.5 Hz, 2H), 6.68 (dt, J = 6.8, 1.1 Hz, 1H), 7.21 (m, 1H), 7.39 (dd, J = 5.9, 1.6 Hz, 2H), 7.61 (dd, J = 8.9, 1.0 Hz, 1H), 8.75 (d, J = 5.9 Hz, 2H).

Step D: 4-(2-Ethyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-3-yl)piperidine, acetic acid salt

A solution of 2-ethyl-3-(4-pyridyl)-imidazo[1,2-a]pyridine (700 mg, 3.13 mmol) in ethanol (12 mL) and acetic acid (4 mL) was hydrogenated using Platinum (IV) oxide (40 mg) under 40 psi of H_2 gas in a Parr shaker at rt for 18 h. The mixture was filtered through celite and concentrated to give the title compound (1.47 g) as a viscous oil.

PROCEDURE 30

4-(2-Benzyloxazol-5-yl)piperidine

Step A: 1-Benzoylisonipecotic acid

To a solution of 10 g of isonipecotic acid in 100 mL of water was added 31 mL of 5 N NaOH at 0 °C. The reaction was warmed to room temperature and stirred for 0.5 h. The reaction was again cooled to 0 °C and 11.97 g of benzoyl chloride was added. The reaction was then warmed to room temperature and stirred for 1.5 h. Concentrated HCl was then added until a precipitate formed. The mixture was extracted with 3x150 mL of ethyl acetate and the combined organic layers were dried over magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was dissolved in methylene chloride. Ether was then slowly added to precipitate the product which was filtered to give 8 g of the title compound. ^1H NMR (500 MHz) ($CDCl_3$): δ 1.83 (m, 3H), 2.10 (m, 1H), 2.65 (m, 1H), 3.12 (m, 2H), 3.79 (m, 1H), 4.53 (m, 1H), 7.38 (m, 5H).

Step B: 4-Hydroxymethyl-1-benzoylpiperidine

To a solution of 2 g of 1-benzoylisonipecotic acid (Step A) in 50 mL THF at 0 °C were added 1.47 g of triethylamine and 1.99 g of isobutyl chloroformate. The reaction was stirred for 1 h at 0 °C. To a solution of 1.10 g of sodium borohydride in 30 mL DMF at 0 °C was slowly added the above THF mixture. The reaction was again stirred for 1 h at 0 °C. Water (80 mL) was slowly added to the reaction and the mixture was extracted 5x80 mL ethyl acetate and the combined organic layers were dried over magnesium sulfate. The solvent was then evaporated under reduced pressure. The residue was purified by flash chromatography with 1:1

hexane : ethyl acetate followed by hexane : ethyl acetate : methanol, 50:50:5 to give 1.865 g of the title compound.
ESI-MS 219.9 (M+H); HPLC A: 2.34 min. (65148-258)

Step C: 1-Benzoylpiperidine-4-carboxaldehyde

To 1.99 g of dimethyl sulfoxide in 45 mL methylene chloride at –78 °C was added 2.16 g of oxalyl chloride. After 10 min, 1.865 g of 4-hydroxymethyl-N-benzoylpiperidine (Step B) in 15 mL of methylene chloride was added at –78 °C and stirred for 30 min. DIEA (5.49 mL) was added and this mixture was stirred for an additional 30 min. at –78 °C and then warmed to room temperature and stirred another 30 min. The reaction was quenched with 50 mL water and extracted with 3x50 mL methylene chloride. The combined organic layers were dried over magnesium sulfate and evaporated under reduced pressure. The residue was chromatographed with 2:1 hexane : ethyl acetate followed by 1:1 hexane : ethyl acetate to give 1.445 g of the title compound.
^{1}H NMR (500 MHz) ($CDCl_3$): δ 1.72 (m, 2H), 1.90 (m, 1H), 2.14 (m, 1H), 2.58 (m, 1H), 3.21 (m, 2H), 3.68 (m, 1H), 4.41 (m, 1H), 7.39 (m, 5H), 9.72 (m, 1H).

Step D: 4-(1-Hydroxy-prop-2-enyl)-1-benzoyl piperidine

To a solution of 500 mg of 1-benzoylpiperidine-4-carboxaldehyde (Step C) in 10 mL THF at –78 °C, was added 2.99 mmol of vinyl magnesium bromide. The solution was warmed to 0 °C and stirred for 1 h. The reaction was quenched with 15 mL of aq. ammonium chloride and extracted with 3x20 mL ether and the combined organic layers were dried over magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography with 2:1 hexane : ethyl acetate followed by 1:1 hexane : ethyl acetate followed by hexane : ethyl acetate : methanol, 50:50:5 to give 411 mg of the title compound.
^{1}H NMR (500 MHz) ($CDCl_3$): δ 1.31 (m, 2H), 1.74 (m, 5H), 2.69 (m, 1H), 2.92 (m, 1H), 4.80 (m, 1H), 3.68 (m, 1H), 5.22 (dd, 2H), 5.84 (m, 1H), 7.43 (m, 5H).

Step E: 4-(1-Phenylacetyoxy-prop-2-enyl)-1-benzoylpiperidine

To 264 mg of 4-(1-hydroxy-prop-2-enyl)-1-benzoylpiperidine (Step D) in 5 mL DMF was added 220 mg of phenyl acetic acid, 292 mg of 1-

hydroxybenzotriazole, 414 mg of EDC, and 419 mg of DIEA. The reaction was stirred at room temperature overnight. The solution was diluted with 50 mL of ether and washed with 2x40 mL water. The aqueous layers were then extracted with 2x 50 mL ether and the combined organic layers were dried over magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography with 4:1 hexane : ethyl acetate followed by 2:1 hexane : ethyl acetate to give 123 mg of the title compound.
ESI-MS 364.1 (M+H).

Step F: 1-Benzoyl-4-(2-benzyloxazol-5-yl)piperidine

Ozone was bubbled through a solution of 120 mg of 4-(1-phenylacetyoxy-prop-2-enyl)-1-benzoylpiperidine (Step E) in 8 mL methylene chloride at –78 °C until the reaction turned blue. To this solution 205 mg of methyl sulfide was added and the reaction was stirred at room temperature overnight. The solvent was evaporated under reduced pressure to give 121 mg of the residue. This residue was dissolved in 3 mL of acetic acid and 76 mg of ammonium acetate was added. The reaction was stirred at 110 °C for 2.5 h, 20 mL of water was added and the mixture was extracted with 3x20 mL methylene chloride. The combined organic layers were dried over magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography with 2:1 hexane: ethyl acetate followed by 1:1 hexane : ethyl acetate followed by hexane: ethyl acetate : methanol, 50:50:5 to give 40 mg of the title compound.
ESI-MS 347.0 (M+H); HPLC A: 3.68 min.

Step G: 4-(2-Benzyloxazol-5-yl)piperidine

To 40 mg of 1-benzoyl-4-(2-benzyloxazol-5-yl)piperidine (step F) in 4.5 mL methanol and 0.5 mL water was added 260 mg of potassium hydroxide. The reaction was stirred at 80 °C overnight, 20 mL of water was added and the mixture was extracted with 3x20 mL ethyl acetate. The combined organic layers were dried over magnesium sulfate. The solvent was evaporated under reduced pressure to give 22 mg of the title compound.
ESI-MS 242.9 (M+H); HPLC A: 2.29 min.

PROCEDURE 31

4-(2-Benzyl-1,3-imidazol-5-yl)piperidine

Step A: 4-Bromoacetyl-1-(t-butoxycarbonyl)piperidine

To a freshly prepared solution of LDA (from diisopropylamine (0.61 g , 6.0 mmol) and n-butyl lithium (2.2 mL, 2.5 M sol'n. In hexane) in 10 mL THF at – 78 °C was added a solution of 4-acetyl-1-(t-butoxycarbonyl) piperidine (1.0 g, 4.7 mmol) in 2.0 mL THF and the resultant mixture was stirred for 20 min. A mixture of trimethylsilyl chloride and triethylamine(1.37 mL, 10.8 mmol and 2.16 mL, 15.5 mmol) was added and the reaction mixture was gradually warmed to rt and stirred for an additional 1h. All the volatile were removed and the crude silyl enol ether was dissolved in 10 mL of THF and the mixture was cooled to 0 °C. To this mixture was added in succession propylene oxide (1.0 mL) and NBS (1.0 g) and the mixture was stirred for 15 min, quenched with a saturated sodium bicarbonate followed by extraction with methylene chloride. The methylene chloride layer was washed with brine, dried, evaporated and purified by silica column chromatography. Elution with methylene chloride and ether (19 :1) gave the title compound (1.11 g) as a yellow solid.

^{1}HNMR (500MHz, $CDCl_3$): δ 4.16 (s, 2H), 4.12 (m, 2H), 2.79-2.84 (m, 3H), 1.47 (s, 3H).

Step B: 4-(2-(2,6-Dichlorobenzyl)-1,3-imidazol-5-yl)-1-(t-butoxycarbonyl)piperidine

A mixture of the bromo compound (0.4 g, 1.36 mmol) from Step A and 2, 6-dichlorophenylacetamidine (0.55 g, 2.7 mmol) in 30 mL of chloroform was refluxed for 4 h. The reaction mixture was filtered. The filtrate was evaporated and purified by silica column chromatography. Elution with hexane: ethyl acetate: methanol 49:49:2 gave (0.28 g) of the title compound.

^{1}HNMR (500 MHz, $CDCl_3$): δ 7.35-7.15 (m, 3H), 6.55 (s, 1H), 4.45 (s, 2H), 4.14 (br, 2H), 2.81-2.69 (m, 3H), 1.46 (s, 3H).

Step C: 4-((2-Benzyl)-1,3-imidazol-5-yl)-1-(t-butoxycarbonyl)piperidine

A mixture of 4-(2-(2,6-dichlorobenzyl)-1,3-imidazol-5-yl)-1-(t-butoxycarbonyl)piperidine (0.51 g, 1.24 mmol) from Step B, Pd/C (0.13g) and ammonium formate (1.5 g, 24.8 mmol) in 8 mL of methanol was refluxed for 30 min. The reaction mixture was filtered and the filtrate was evaporated. The residue was partitioned between methylene chloride and water (200 mL). The methylene chloride

layer was washed with brine, dried , evaporated and purified by silica column chromatography. Elution with 3% methanol-methylene chloride gave (0.35 g) of the title compound.
^{1}HNMR (500 MHz, $CDCl_3$): δ 7.34-7.22 (m, 5H), 6.58 (s, 1H), 4.18 (br, 2H), 4.08 (s, 2H), 2.71 (br, 2H), 2.68 (m,1H), 1.47 (s, 3H).

Step D: 4-(2-Benzyl-1,3-imidazol-5-yl)piperidine hydrochloride
To 4-((2-benzyl)-1,3-imidazol-5-yl)-1-(t-butoxycarbonyl) piperidine (0.16 g) from Step C in 2 mL of ethyl acetate at 0 °C was added a 2 mL saturated solution of HCl in ethyl acetate. The reaction mixture was stirred for 30 min. Evaporation of ethyl acetate followed by trituration of the resultant oil gave (0.15 g) of the title compound.
^{1}HNMR (500 MHz, CD_3OD): δ 7.40-7.29 (m, 6H), 4.32 (s, 2H), 3.49 (m, 2H), 3.31-3.01 (m, 3H), 2.24 (m, 2H), 1.92 (m, 2H).

PROCEDURE 32

4-((2-Benzyl-4-ethyl)-1,3-imidazol-5-yl)piperidine

Step A: 4-((2-Benzyl-4-iodo)-1,3-imidazol-5-yl)-1-(t-butoxycarbonyl)piperidine
To a mixture of 4-((2-benzyl)-1,3-imidazol-5-yl)-1-(t-butoxycarbonyl)piperidine (0.15 g, 0.43 mmol). Iodine (0.16g, 0.65 mmol) and potassium iodide (0.22 g, 1.3 mmol) in 4 mL THF:water (1:1) was added a solution of sodium hydroxide (0.5 mL) and stirred at rt for 30 min. After confirming the completion of reaction by TLC, the reaction was quenched with a saturated solution of sodium thiosulfate and the pH was adjusted to 7-8. The resultant mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with brine, dried, evaporated and purified by silica column chromatography. Elution with 1% methanol-methylene chloride gave (0.17 g) of the title compound.
^{1}HNMR (500 MHz, $CDCl_3$): δ 7.32-7.22 (m, 5H), 4.13 (br, 2H), 4.06 (s, 2H), 2.74 (m, 3H), 1.47 (s, 3H).

Step B: 4-((2-Benzyl-4-ethenyl)-1,3-imidazol-5-yl)-1-(t-butoxycarbonyl)piperidine

A mixture of 4-((2-benzyl-4-iodo)-1,3-imidazol-5-yl)-1-(t-butoxycarbonyl)piperidine (0.17 g, 0.36 mmol) from Step A, tri-n-butyl vinyltin (0.17g, 0.54 mmol) and tetrakistriphenylphosphinyl palladium (0.020 g) in 4 mL toluene was stirred at 100-110 °C until the completion of reaction by TLC. Evaporation of the volatiles followed by purification by silica column and elution with 1% methanol-methylene chloride gave (0.061 g) of the title compound. ^{1}HNMR (500 MHz, $CDCl_3$): δ 7.36-7.26 (m, 5H), 6.61-6.55 (m,1H), 5.10 (m, 2H), 4.33 (br, 2H), 4.13 (s, 2H), 1.47(s, 3H).

Step C: 4-((2-Benzyl-4-ethyl)-1,3-imidazol-2-yl)-1-(t-butoxycarbonyl)piperidine

A mixture of 4-((2-benzyl-4-ethenyl)-1,3-imidazol-5-yl)-1-(t-butoxycarbonyl)piperidine (0.073 g) from Step B in 3.0 mL methanol was hydrogenated over Pd/C (5 mg) at rt. Evaporation of the volatiles followed by purification by preparative silica chromatography and elution with 1% methanol–methylene chloride gave (0.043 g) of the title compound. ^{1}HNMR (500 MHz, $CDCl_3$): δ 7.31-7.20 (m, 5H), 4.19 (br, 2H), 4.01 (s, 2H), 2.74-2.66 9m, 3H), 2.51 (q, 2H), 1.46(s, 3H), 1.15 (t, 3H).

Step D: 4-((2-Benzyl-4-ethyl)-1,3-imidazol-2-yl)piperidine di-hydrochloride

To 4-((2-benzyl-4-ethyl)-1,3-imidazol-2-yl)-1-(t-butoxycarbonyl)piperidine (0.043 g) from Step C in 1.0 mL ethyl acetate at 0 °C was added a 2.0 mL saturated solution of HCl in ethyl acetate. The reaction mixture was stirred for 30 min. Evaporation of ethyl acetate followed by trituration of the resultant oil gave (0.038 g) of the title compound.

PROCEDURE 33

4-(2-Ethyl-4,5,6,7-tetrahydro-(2H)-indazol-3-yl)-1-piperidine

Step A: (1-Benzylpiperidin-4-yl)-(cyclohexanon-2-yl)ketone

To a suspension of 1.60 g 60% sodium hydride in 10 mL dry THF was added a solution of 1.963 g (20 mmole) cyclohexanone and 9.893 g (40 mmole) of 1-benzylpiperidine-4-carboxylic acid ethyl ester in 30 mL THF. This mixture was

heated to reflux over night. Work-up followed by silica gel FC (15~50% ethyl acetate in hexanes with 1% triethylamine) provided 4.4 g product containing about 5.7:1 molar ratio of starting 1-benzylpiperidine-4-carboxylic acid ethyl ester and title compound.

ESI-MS 300.3 (M+H), HPLC A: 2.90 and 3.57 min. (for tautomeric forms).

Step B: 4-(2-Ethyl-4,5,6,7-tetrahydro-(2H)-indazol-3-yl)-1-benzylpiperidine

The title compound was prepared from the semi-crude (1-benzylpiperidin-4-yl)-(cyclohexanon-2-yl)ketone from step A and 34% aqueous ethylhydrazine in 4:1 acetonitrile and water at room temperature. This provided 8:1 ratio of isomeric ethyl pyrazoles in favor of the title compound. (Note: Use of ethyl hydrazine oxalate in the presence of DIEA gave about 2:1 ratio of the same isomers.) The 1-benzylpiperidine-4-carboxylic acid ethyl ester present in the starting β–diketone was removed after saponification of the crude product with sodium hydroxide in water ethanol mixture followed by extractive work-up. The desired ethyl isomer is the higher R_f isomer. It was isolated on silica gel chromatography (60~100% ethyl acetate in hexanes and 5~20% methanol in ethyl acetate, both with 1% triethylamine).

^{1}H NMR (500 MHz) δ 7.33~7.36 (m, 4H), 7.26~7.30 (m, 1H), 4.07 (q, 7.2 Hz, 2H), 3.57 (s, 2H), 3.00~3.03 (m, 2H), 2.64~2.66 (m, 2H), 2.60~2.63 (m, 2H), 2.57~2.63 (m, 1H), 1.96~2.08 (m, 4H), 1.69~1.81 (m, 6H), 1.39 (t, 7.2 Hz, 3H). The identity of the title compound was confirmed by NOE difference spectroscopy.

Step C: 4-(2-Ethyl-4,5,6,7-tetrahydro-(2H)-indazol-3-yl)piperidine

A mixture of 0.273 g 4-(2-ethyl-4,5,6,7-tetrahydro-(2H)-indazol-3-yl)-1-benzylpiperidine from Step B above, 0.789 g ammonium formate, and 35 mg 20% $Pd(OH)_2$ in 6 mL methanol was heated at 65 °C for 1 h. Basic aqueous work-up with ether extraction provided 0.192 g title compound as a colorless solid (97%).

^{1}H NMR (500 MHz) δ 4.08 (q, 7.2 Hz, 2H), 3.19 (br d, 11.9 Hz, 2H), 2.71~2.77 (m, 1H), 2.68~2.74 (m, 2H), 2.64~2.66 (m, 2H), 2.60~2.62 (m, 2H), 1.82~1.91 (m, 2H), 1.71~1.80 (m, 6H), 1.40 (t, 7.2 Hz, 3H). The identity of the title compound was confirmed again by NOE difference spectroscopy.

PROCEDURE 34

4-(4,5,6,7-Tetrahydro-(2H)-indazol-3-yl)-1-piperidine

Step A: 4-(4,5,6,7-Tetrahydro-(2H)-indazol-3-yl)-1-benzyl piperidine, trifluoroacetic acid salt

The title compound was prepared using a procedure similar to that in Procedure 33, Step B with hydrazine instead of ethyl hydrazine. It was further purified on HPLC.

^{1}H NMR (500 MHz, CD_3OD) δ 7.47~7.55 (m, 5H), 4.35 (s, 2H), 3.61 (br d, 12.3 Hz, 2H), 3.13~3.21 (m, 3H), 2.71~2.73 (m, 2H), 2.56~2.58 (m, 2H), 2.17 (br d, 13.3 Hz, 2H), 2.04~2.12 (m, 2H), 1.79~1.89 (m, 4H). ESI-MS 296.3 (M+H), HPLC A: 2.33 min.

Step B: 4-(4,5,6,7-Tetrahydro-(2H)-indazol-3-yl)piperidine

The title compound was prepared using a procedure similar to that in Procedure 33, Step C as a white solid.

^{1}H NMR (500 MHz) δ 3.20 (br d, 12.4 Hz, 2H), 2.72~2.797 (m, 3H), 2.64~2.66 (m, 2H), 2.49~2.52 (m, 2H), 1.87~1.90 (m, 2H), 1.70~1.84 (m, 6H). ESI-MS 206.2 (M+H), HPLC A: 0.80 min.

PROCEDURE 35

3,3-Difluoro-3-(2-pyridyl)propyl)piperidine

Step A: Ethyl oxo(2-pyridyl)acetate

A solution of *n*-butyl lithium (100 mL, 1.6 M, 160 mmol) in hexanes was added over 2 min. to a stirred solution of 2-bromopyridine (15.0 mL, 24.9 g, 157 mmol) in 500 mL of ether cooled in a dry ice/isopropanol bath, causing a temporary rise in temperature to -47 °C. After 25 min., the solution was transferred rapidly to a stirred 0 °C solution of diethyl oxalate (75 mL, 81 g, 550 mmol) in 1000 mL of ether. After 2 h at 0 °C, the mixture was washed with saturated aq. sodium bicarbonate (900 mL), water (900 mL), and saturated aq. brine (450 mL). The organic layer was dried (magnesium sulfate), filtered, and evaporated. Distillation gave the title compound as 11.68 g of yellow liquid, B.p. 96-108 °C (0.3 mm Hg pressure). For the title compound:

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.78 (d, J = 5, 1H), 8.13 (d, J = 8, 1H), 7.93 (td, J = 8, 2, 1H), 7.56 (ddd, J = 8, 5, 1, 1H), 4.51 (q, J = 7, 2H), 1.44 (t, J = 7, 3H).

Step B: Ethyl difluoro(2-pyridyl)acetate

Ethyl oxo(2-pyridyl)acetate (11.59 g, 64.7 mmol, from Procedure 35, Step A) was added to a flask containing (diethylamino)sulfur trifluoride (18.0 mL, 22.0 g, 136 mmol) and the solution was heated to 45 °C overnight. An additional portion of (diethylamino)sulfur trifluoride (24.9 g, 154 mmol) was added and the solution was heated to 55 °C for 2 days. After cooling to rt, the solution was added carefully to a stirred mixture of ethyl acetate (600 mL), ice (500 g), water (500 mL), and sodium bicarbonate (100 g). After the resulting reaction had subsided, the layers were separated and the organic layer was washed with 250 mL each of saturated aq. sodium bicarbonate, water, and saturated aq. brine. The organic layer was dried (sodium sulfate), decanted, and evaporated. Distillation gave 8.45 g of yellow liquid, B.p. 50-63 °C (0.1 mm Hg), containing a residual impurity. Further purification by flash column chromatography on silica gel, eluting with 80:20 v/v to 75:25 v/v hexanes/ethyl acetate, gave the title compound as 6.54 g of yellow oil. For the title compound:

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (d, J = 5, 1H), 7.88 (td, J = 8, 2, 1H), 7.76 (d, J = 8, 1H), 7.44 (dd, J = 8, 5, 1H), 4.40 (q, J = 7, 2H), 1.35 (t, J = 7, 3H).

Step C: 1-(t-Butoxycarbonyl)-4-(3,3-difluoro-3-(2-pyridyl)prop-1-en-1-yl)piperidine

Ethyl difluoro(2-pyridyl)acetate (1.00 g, 4.97 mmol, from Procedure 35, Step B) was dissolved in CH_3OH (15 mL) in a 3-neck round bottom flask fitted with a mechanical stirrer, and the resulting solution was cooled in a dry ice/isopropanol bath. Sodium borohydride (114 mg, 3.0 mmol) was added in 2 portions 15 min. apart. After an additional 55 min., the cold reaction was quenched by the addition of saturated aq. ammonium chloride (6.5 mL) over 12 min. After 10 min., the cooling bath was removed and the mixture was stirred for 35 min. before being diluted with saturated aq. brine (100 mL) and extracted with ethyl acetate (4x75 mL). The combined organic layers were dried (sodium sulfate), decanted, and evaporated to give 1.02 g of crude 2,2-difluoro-2-(2-pyridyl)-1-methoxyethanol as an amber oil.

A suspension of ((1-(t-butoxycarbonyl)piperidin-4-yl)methyl)triphenylphosphonium iodide (5.29 g, 9.00 mmol, from Procedure 17, Step C) in THF (70 mL) was stirred at rt for 40 min. A toluene solution of potassium bis(trimethylsilyl)amide (18 mL, 0.5 M, 9.0 mmol) was added, giving an orange suspension. After 40 min., crude 2,2-difluoro-2-(2-pyridyl)-1-methoxyethanol (940 mg, 4.97 mmol) was added in THF (20 mL). After an additional 50 min., the mixture was quenched by the addition of saturated aq. NH_4Cl (10 mL). The mixture was partitioned between ethyl acetate (100 mL) and water (100 mL), and the aqueous layer was extracted with ethyl acetate (3x100 mL). The organic layers were washed in succession with saturated aq. brine (100 mL), dried (sodium sulfate), decanted, and evaporated. Purification by flash column chromatography on silica gel, eluting with 90:10 v/v to 80:20 v/v hexanes/ethyl acetate, gave 1.18 mg of the title compound (approximately 95:5 cis/trans mixture) as an oil which solidified upon standing. For the title compound:

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (d, J = 5, 1H), 7.84 (td, J = 8, 2, 1H), 7.70 (d, J = 8, 1H), 7.39 (dd, J = 8, 5, 1H), 5.93 (td, J = 14, 11, 1H), 5.70 (ddt, J = 11, 10, 2, 1H), 4.17-3.99 (bs, 2H), 2.80-2.62 (m, 3H), 1.58 (d, J = 12, 2H), 1.46 (s, 9H), 1.26 (qd, J = 12, 4, 2H).

ESI-MS 339 (M+H); HPLC A: 4.28 min.

Step D: 1-(t-Butoxycarbonyl)-4-(3,3-difluoro-3-(2-pyridyl)propyl)piperidine

Potassium azodicarboxylate (246 mg, 1.27 mmol) was added to a stirred solution of 1-(t-butoxycarbonyl)-4-(3,3-difluoro-3-(2-pyridyl)prop-1-enyl)piperidine (143 mg, 0.42 mmol, from Procedure 35, Step C) in methanol (1.4 mL) at rt. A solution (0.58 mL) of 75:25 v/v CH_3OH/AcOH was added in three portions at 30-min. intervals. After two h, an additional portion of potassium azodicarboxylate (246 mg, 1.27 mmol) was added, followed by a solution (0.58 mL) of 75:25 v/v CH_3OH/AcOH added in three portions at 30-min. intervals. After another two h, a third portion of potassium azodicarboxylate (246 mg, 1.27 mmol) was added, followed by a solution (0.58 mL) of 75:25 v/v CH_3OH/AcOH added in the same manner as before. After stirring overnight, the mixture was diluted with ethyl acetate (50 mL) and washed with saturated aq. sodium bicarbonate (30 mL) followed by saturated aq. brine (30 mL). The organic layer was dried (sodium sulfate), decanted, and evaporated to give the crude product containing approximately 30%

starting olefin. This material was combined with crude product similarly obtained from 1-(t-butoxycarbonyl)-4-(3,3-difluoro-3-(2-pyridyl)prop-1-enyl)piperidine (20 mg, 0.059 mmol) and purified by preparative HPLC on a 20x250 mm Chiracel OD column, eluting with 98:2 v/v hexanes/isopropanol, to give 105 mg of the title compound:

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (d, J = 5, 1H), 7.82 (td, J = 8, 2, 1H), 7.64 (d, J = 8, 1H), 7.38 (dd, J = 8, 5, 1H), 4.17-4.00 (bs, 2H), 2.75-2.62 (m, 2H), 2.42-2.30 (m, 2H), 1.67 (d, J = 12, 2H), 1.46 (s. 9H), 1.45-1.38 (m, 3H), 1.15-1.04 (m, 2H).
ESI-MS 241 (M+H-100); HPLC A: 4.36 min.

Step E: 4-(3,3-Difluoro-3-(2-pyridyl)propyl)piperidine

The title compound was prepared using procedures analogous to those described in Procedure 17, Step H, substituting 1-(t-butoxycarbonyl)-4-(3,3-difluoro-3-(2-pyridyl)propyl)piperidine (from Procedure 35, Step D) for 1-(t-butoxycarbonyl)-4-(3,3-difluoro-3-(4-fluorophenyl)propyl)piperidine. For the title compound:
^{1}H NMR (500 MHz, CD_3OD) δ 8.62 (d, J = 5, 1H), 7.95 (td, J = 8, 2, 1H), 7.68 (d, J = 8, 1H), 7.50 (dd, J = 8, 5, 1H), 2.99 (d, J = 12, 2H), 2.53 (td, J = 12, 3, 2H), 2.37-2.26 (m, 2H), 1.67 (d, J = 12, 2H), 1.42-1.28 (m, 3H), 1.08 (dq, J = 12, 4, 2H).
ESI-MS 241 (M+H); HPLC A: 2.21 min.

PROCEDURE 36

4-(3,3-Difluoro-3-(6-methylpyridazin-3-yl)propyl)piperidine

Step A: 3-Bromo-6-methylpyridazine

A solution (3.0 mL) containing 30%HBr in acetic acid was added to 3-(trifluoromethanesulfonyloxy)-6-methylpyridazine (prepared as described by M. Rohr, *et al.*, *Heterocycles*, **1996**, *43*, 1459-64) and the mixture was heated in a 100 °C oil bath for 2.5 h. The mixture was cooled in an ice bath, adjusted to pH ≥ 9 (as determined using pH paper) by the careful addition of 20% aqueous NaOH, and extracted with ether (3x20 mL). The organic layers were dried (sodium sulfate), decanted, and evaporated to give title compound as 359 mg of pale tan crystals. For the title compound:
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, J = 9, 1H), 7.22 (d, J = 9, 1H), 2.70 (s, 3H).

Step B: Ethyl difluoro(6-methylpyridazin-3-yl)acetate

This procedure is derived from the general method of T. Taguchi, *et al.* (*Tetrahedron Lett.*, **1986**, *27*, 6103-6106). Ethyl difluoroiodoacetate (0.355 mL, 651 mg, 2.60 mmol) was added to a rapidly stirred suspension of copper powder (333 mg, 5.24 mmol) in DMSO (6.5 mL) at rt. After 50 min., 3-bromo-6-methylpyridazine (300 mg, 1.73 mmol) was added in DMSO (1.0 mL). After 20 h, the mixture was transferred to a separatory funnel containing water (25 mL) and saturated aq. NH_4Cl (25 mL), and extracted with ethyl acetate (2x50 mL). The organic extracts were washed with saturated aq. brine, dried (sodium sulfate), decanted, and evaporated. Purification by flash column chromatography on silica gel, eluting with 70:30 v/v hexanes/ethyl acetate, gave 363 mg of the title compound as an amber liquid. For the title compound:

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, J = 9, 1H), 7.53 (d, J = 9, 1H), 4.43 (q, J = 7, 2H), 2.82 (s, 3H), 1.38 (t, J = 7, 3H).

Steps C-E: 4-(3,3-Difluoro-3-(6-methylpyridazin-3-yl)propyl)piperidine

The title compound was prepared using procedures analogous to those described in Procedure 35, Steps C-E, substituting ethyl difluoro(6-methylpyridazin-3-yl)acetate (from Procedure 36 Step B) for ethyl difluoro(2-pyridyl)acetate in Step C. For the title compound:

^{1}H NMR (500 MHz, CD_3OD) δ 7.86 (d, J = 9, 1H), 7.74 (d, J = 9, 1H), 2.99 (dm, J = 12, 2H), 2.74 (s, 3H), 2.54 (td, J = 12, 3, 2H), 2.51-2.40 (m, 2H), 1.69 (bd, J = 12, 2H), 1.47-1.34 (m, 3H), 1.10 (qd, J = 12, 4, 2H).

PROCEDURE 37

4-(3,3-Difluoro-3-(5-(trifluoromethyl)pyrid-2-yl)propyl)piperidine

The title compound was prepared using procedures analogous to those described in Procedure 36, substituting 2-bromo-5-(trifluoromethyl)pyridine for 3-bromo-6-methylpyridazine in Step B. For the title compound:

^{1}H NMR (500 MHz, CD_3OD) δ 8.96 (s, 1H), 8.28 (dd, J = 8, 2, 1H), 7.88 (d, J = 8, 1H), 2.99 (bd, J = 12, 2H), 2.53 (td, J = 12, 2, 2H), 2.43-2.31 (m, 2H), 1.68 (bd, J = 13, 2H), 1.44-1.28 (m, 3H), 1.09 (qd, J = 12, 3, 2H);

ESI-MS 309 (M+H); HPLC A: 2.32 min.

PROCEDURE 38

4-(3,3-Difluoro-3-(3-pyridyl)propyl)piperidine

Step A: Dimethyl (2-oxo-2-(3-pyridyl)ethyl)phosphonate

A solution of *n*-butyl lithium in hexanes (9.0 mL, 1.6 M, 14 mmol) was added over 10 min. to a solution of dimethyl methylphosphonate (1.50 mL, 1.72 g, 13.8 mmol) in THF (60 mL) cooled in a dry ice/isopropanol bath. After 30 min., a solution of methyl nicotinate (757 mg, 5.52 mmol) in THF (6 mL) was added over 2 min. The solution was stirred in the cooling bath for 45 min. before being allowed to warm to 0 °C over 1 h. The reaction was quenched with saturated aq. NH_4Cl (50 mL) and then partitioned between saturated aq. brine (50 mL) and methylene chloride (200 mL). The aq. layer was extracted with methylene chloride (2x100 mL). The combined organic layers were dried (sodium sulfate) decanted, and evaporated. Purification by flash column chromatography on silica gel, eluting with ethyl acetate followed by 97:3 v/v methylene chloride/CH_3OH, gave material containing some residual impurity. Further purification by flash column chromatography on silica gel, eluting with 50:50:5 v/v/v to 50:50:10 v/v/v toluene/ethyl acetate /CH_3OH gave 1.15 g of the title compound. For the title compound:
^1H NMR (500 MHz, $CDCl_3$) δ 9.26-9.20 (bs, 1H), 8.83 (d, J = 4, 1H), 8.34 (dt, J = 8, 2, 1H), 7.70 (dd, J = 8, 4, 1H), 3.82 (d, J = 11, 6H), 3.67 (d, J = 24, 2H).

Step B: 1-(t-Butoxycarbonyl)-4-(3-oxo-3-(3-pyridyl)prop-1-enyl)piperidine

1,1,1-Triacetoxy-1,1-dihydro-1,2-benzoiodoxol-3(1H)-one (750 mg, 1.77 mmol) was added to a solution of 1-(t-butoxycarbonyl)-4-(hydroxymethyl)piperidine (339 mg, 1.57 mmol, from Procedure 17, Step A) in methylene chloride (10 mL) and the mixture was stirred at rt. After 45 min., and additional portion of 1,1,1-triacetoxy-1,1-dihydro-1,2-benzoiodoxol-3(1H)-one (150 mg, 0.35 mmol) was added. After an additional 30 min., ether (30 mL) and 1.3 N NaOH (10 mL) were added and stirring was continued for 20 min. The mixture was transferred to a separatory funnel with additional ether (30 mL) and 1.3 N NaOH (15 mL). The organic layer was separated, washed with water (20 mL), dried (sodium sulfate), decanted, and evaporated to give 291 mg of 1-(t-butoxycarbonyl)-4-piperidinecarboxaldehyde as a colorless oil.

A solution of dimethyl (2-oxo-2-(3-pyridyl)ethyl)phosphonate (150 mg, 0.65 mmol, from Procedure 38, Step A) in THF (1.8 mL) was added to a stirred

suspension of sodium hydride (60% oil dispersion, 15 mg of sodium hydride, 0.63 mmol) in THF (3.0 mL). The resulting suspension was warmed in a 45 °C oil bath for 30 min. After the mixture had cooled to rt, 1-(t-butoxycarbonyl)-4-piperidinecarboxaldehyde (112 mg, 0.53 mmol) was added in THF (1.5 mL). After stirring overnight at rt, the mixture was diluted with ether (20 mL) and washed with 2.5 N NaOH (20 mL) followed by saturated aq. brine (20 mL). The aq. layers were extracted in succession with ether (20 mL), and the combined organic layers were dried (sodium sulfate), decanted, and evaporated. Purification by flash column chromatography on silica gel, eluting with 80:20 v/v to 60:40 v/v hexanes/ethyl acetate, gave 135 mg of the title compound (trans isomer) as a yellow syrup. For the title compound:

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.17-9.13 (bs, 1H), 8.81 (bd, J = 4, 1H), 8.27 (d, J = 8, 1H), 7.49 (dd, J = 8, 4, 1H), 7.07 (dd, J = 15, 7, 1H), 6.85 (dd, J = 15, 1, 1H), 4.25-4.13 (bs, 2H), 2.87-2.78 (m, 2H), 2.51-2.41 (m, 1H), 1.83 (d, J = 12, 2H), 1.49 (s, 9H), 1.45 (qd, J = 12, 4, 2H).

ESI-MS 261 (M+H-56), 217 (M+H-100); HPLC A: 1.73 min.

Step C: 1-(t-Butoxycarbonyl)-4-(3-oxo-3-(3-pyridyl)propyl)piperidine

1-(t-Butoxycarbonyl)-4-(3-oxo-3-(3-pyridyl)prop-1-enyl)piperidine (940 mg, 2.97 mmol, from Procedure 38, Step B) was hydrogenated using 5% Pd/C in 95% ethanol at atmospheric pressure. Purification by flash column chromatography on silica gel, eluting with 90:10 v/v to 50:50 v/v hexanes/ethyl acetate gave 884 mg of the title compound as a colorless syrup. For the title compound:

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.23-9.15 (bs, 1H), 8.81 (bd, J = 4, 1H), 8.28 (dt, J = 8, 1, 1H), 7.48 (dd, J = 8, 4, 1H), 4.19-4.04 (bs, 2H), 3.04 (t, J = 8, 2H), 2.70 (bt, J = 11, 2H), 1.78-1.70 (m, 4H), 1.56-1.45 (m, 1H), 1.47 (s, 9H), 1.17 (qd, J = 12, 4, 2H).

ESI-MS 263 (M+H-56), 219 (M+H-100); HPLC A: 1.78 min.

Step D: 1-(t-Butoxycarbonyl)-4-(3,3-difluoro-3-(3-pyridyl)propyl)piperidine

A solution of 1-(t-butoxycarbonyl)-4-(3-oxo-3-(3-pyridyl)propyl)piperidine (810 mg, 2.54 mmol, from Procedure 38, Step C) in (diethylamino)sulfur trifluoride (3.30 mL, 3.66 g, 23 mmol) was stirred in a teflon tube at 40 °C for 2 days. The reaction was diluted with methylene chloride (20 mL) and the resulting solution was added in portions to a stirred mixture of water (150

mL), ice (150 g) and sodium bicarbonate (29.3 g). After the resulting reaction had subsided, the mixture was extracted with ethyl acetate (2x200 mL). The organic layers were washed in succession with saturated aq. brine (100 mL), dried (sodium sulfate), decanted, and evaporated. Flash column chromatography on silica gel, eluting with 80:20 v/v to 50:50 v/v toluene/ether, gave material containing some residual impurity. Further purification by preparative HPLC on a 20x250 mm Chiracel OD column, eluting with 80:20 v/v hexanes/isopropanol, gave 395 mg of the title compound:

^{1}H NMR (500 MHz, CD_3OD) δ 8.69 (s, 1H), 8.64 (d, J = 5, 1H), 7.97 (d, J = 8, 1H), 7.54 (dd, J = 8, 5, 1H), 4.04 (d, J = 13, 2H), 2.78-2.62 (bs, 2H), 2.31-2.20 (m, 2H), 1.68 (d, J = 12, 2H), 1.50-1.40 (m, 1H), 1.43 (s, 9H), 1.40-1.34 (m, 2H), 1.02 (qd, J = 12, 4, 2H).

ESI-MS 285 (M+H-56), 241 (M+H-100); HPLC A: 2.10 min.

Step E: 4-(3,3-Difluoro-3-(3-pyridyl)propyl)piperidine

The title compound was prepared using procedures analogous to those described in Procedure 17, Step H, substituting 1-(t-butoxycarbonyl)-4-(3,3-difluoro-3-(3-pyridyl)propyl)piperidine (from Procedure 38, Step D) for 1-(t-butoxycarbonyl)-4-(3,3-difluoro-3-(4-fluorophenyl)propyl)piperidine. For the title compound:

^{1}H NMR (500 MHz, CD_3OD) δ 8.68 (s, 1H), 8.64 (d, J = 4, 1H), 7.97 (d, J = 8, 1H), 7.54 (dd, J = 8, 4, 1H), 2.98 (bd, J = 12, 2H), 2.52 (td, J = 12, 3, 2H), 2.30-2.18 (m, 2H), 1.66 (bd, J = 13, 2H), 1.44-1.30 (m, 3H), 1.08 (qd, J = 12, 3, 2H); ESI-MS 241 (M+H).

PROCEDURE 39

4-(3,3-Difluoro-3-(1-methylpyrazol-4-yl)propyl)piperidine

The title compound was prepared using procedures analogous to those described in Procedure 38, substituting ethyl 1-methyl-4-pyrazolecarboxylate, obtained by methylation of ethyl 4-pyrazolecarboxylate with iodomethane and K_2CO_3 in CH_3CN at rt, for methyl nicotinate in Step A. For the title compound:

^{1}H NMR (500 MHz, CD_3OD) δ 7.78 (s, 1H), 7.54 (s, 1H), 3.89 (s, 3H), 3.00 (dt, J = 12, 3, 2H), 2.55 (td, J = 12, 3, 2H), 2.22-2.10 (m, 2H), 1.69 (bd, J = 12, 2H), 1.45-1.34 (m, 3H), 1.10 (qd, J = 12, 4, 2H).

ESI-MS 244 (M+H, 60%), 224 (M-19, 100%); HPLC A: 0.98 min.

PROCEDURE 40

4-(7-Chloroimidazo[1,2-a]pyridin-3-yl)piperidine, TFA salt

The title compound was prepared from 350 mg of 1-(t-butoxycarbonyl)-4-(1-bromo-2-oxoethyl)piperidine (from Procedure , Step C) and 162 mg of 2-amino-4-chloropyridine (prepared using procedures analogous to those described by R.J. Sundberg *et al, Org. Preparations & Procedures Int.*. **1997**, 29, (1), 117-122) in 10 mL ethanol using a procedure analogous to that described in Procedure 27, Step A - B to provide 240 mg of the BOC intermediate as a solid prior to the final de-BOC to give the title TFA salt.

PROCEDURE 41

4-(7-n-Propylimidazo[1,2-a]pyridin-3-yl)piperidine, TFA salt

The title compound was prepared according to the general procedures of Procedure 27 and 28, employing 2-amino-4-n-propylpyridine (prepared using a procedure analogous to that described in Procedure 28, Step A) in place of 2-aminopyridine in Procedure 27, Step A.

PROCEDURE 42

4-(6-Fluoroimidazo[1,2-a]pyridin-3-yl)piperidine, TFA salt

The title compound was prepared from 1-(t-butoxycarbonyl)-4-(1-bromo-2-oxoethyl)piperidine (from Procedure 23, Step B) and 2-amino-5-fluoropyridine (prepared using procedures analogous to those described by D.C. Baker *et al, Synthesis.* **1989**, 905) using a procedures similar to that described in Procedure 27, Step A - C.

For the BOC intermediate:

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.51 (s, 9H), 1.60-1.80 (m, 2H), 2.07 (br d, 2H), 2.85-3.00 (m, 3H), 4.20-4.40 (br, 2H), 7.11 (m, 1H), 7.47 (s, 3H), 7.60(m, 1H), 7.89 (m, 1H).

PROCEDURE 43

4-(6-Fluoro-7-methylimidazo[1,2-a]pyridin-3-yl)piperidine The title compound was prepared using procedures analogous to those described in Procedure 27, Step A - C, except 2-amino-5-fluoro-4-methylpyridine (prepared using procedures analogous to

those described by D.C. Baker *et al, Synthesis.* **1989**, 905) was employed in place of 2-amino-5-fluoropyridine in Step A.

PROCEDURE 44

4-(2-Ethylindazol-3-yl)piperidine, TFA salt

Step A: 2-Ethylindazole

To a solution of indazole (6.2 g, 52.5 mmol) in DMF (30 mL) was added sodium hydride (60 % dispersion in mineral oil, 3.0 g, 75.0 mmol) at 0 °C. After stirring at 0 °C for 20 min., ethyl iodide (5 mL, 62.5 mmol) was added dropwise at 0 °C. The mixture was stirred at rt for 1 h, and then partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate (3X). The combined organic phases were washed with brine, and dried over anhydrous magnesium sulfate. TLC indicated that a 2 : 1 mixture of two isomers was formed. The mixture was purified by flash chromatography (hexanes : ethyl acetate = 4 : 1, then 1 : 1) to give 2.34 g of the title compound as a viscous oil (slow moving isomer).

Step B: 2-Ethyl-3-bromoindazole

To a solution of 2-ethylindazole (2.32 g, 15.87 mmol) in ethanol (20 mL) was added bromine (2.54 g, 15.87 mmol) in ethanol (1 mL)/water (1 mL) at 0 °C. After stirring at 0 °C for 10 min. and at rt for 1h, the reaction was quenched with aq. sodium bicarbonate. The mixture was partitioned between ethyl acetate and aq. sodium bicarbonate. The aqueous layer was extracted with ethyl acetate (3X). The combined organic phase was washed with brine, and dried over anhydrous magnesium sulfate. Purification by flash chromatography (hexanes : ethyl acetate = 1 : 1, then 100 % ethyl acetate) gave 2.34 g of the title compound as a viscous oil.

Step C: 1-(t-Butoxycarbonyl)-4-hydroxy-4-(2-ethyl-indazol-3-yl)piperidine

To a solution of 2-ethyl-3-bromoindazole (3.4 g, 15.18 mmol) in THF (30 mL) was added t-BuLi (1.7 M in pentane, 10.72 mL, 18.22 mmol) dropwise at –78 °C. After stirring at –78 °C for 20 min., was added *tert*-butyl 4-oxo-1-piperidinecarboxylate (3.03 g, 15.18 mmol) in THF (10 mL) dropwise at –78 °C. The mixture was stirred at –78 °C for 10 min. and at rt for 18 h. After the reaction was

quenched with aq. NH_4Cl , the mixture was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate (3X). The combined organic phases were washed with brine, and dried over anhydrous magnesium sulfate. Concentration followed by purification by flash chromatography (hexanes ethyl acetate = 4 : 1, then 1 : 1) to give 1.18 g of the title compound as a foamy solid.

Step D: 1-(t-Butoxycarbonyl)-4-(2-ethyl-indazol-3-yl)-[1,2,3,6]tetrahydropyridine

To a solution of 1-(t-butoxycarbonyl)-4-hydroxy-4-(2-ethyl-indazol-3-yl)piperidine (651 mg, 1.89 mmol) in toluene (5 mL) was added (methoxycarbonylsulfamoyl)-triethylammonium hydroxide inner salt (540 mg, 2.27 mmol). After heating up to ~70 °C for 10 min., was added additional 5 mL of toluene. The mixture was stirred at 70 °C for additional 2h. The mixture was partitioned between ethyl acetate and aq. sodium bicarbonate. Aqueous layer was extracted with ethyl acetate (3X). The combined organic phases were washed with brine, and dried over anhydrous magnesium sulfate. Concentration followed by purification by flash chromatography (hexanes : ethyl acetate = 4 : 1, then 1 : 1) gave 514 mg of the title compound as a viscous oil.

Step E: 1-(t-Butoxycarbonyl)-4-(2-ethyl-[5,6,7,8]tetrahydroindazol-3-yl)piperidine

A solution of 1-(t-butoxycarbonyl)-4-(2-ethyl-indazol-3-yl)-[1,2,3,6]tetrahydropyridine (500 mg, 1.53 mmol) in methanol (5 mL) was hydrogenated using $Pd(OH)_2$ (100 mg) under atmospheric H_2 for 4.5 h. After the addition of Platinum (IV) oxide (100 mg) hydrogenation was continued for additional 4h. The mixture was filtered through celite and concentrated to give the title compound (461 mg) as a viscous oil. ESI-MS 333 (M+1); HPLC A: 2.45 min.

Step F: 1-(t-Butoxycarbonyl)-4-(2-ethylindazol-3-yl)piperidine

To a solution of 1-(t-butoxycarbonyl)-4-(2-ethyl-[5,6,7,8]tetrahydroindazol-3-yl)piperidine (80 mg, 0.24 mmol) in toluene (3 mL) was added DDQ (115 mg, 0.51 mmol) at rt. After refluxing for 4 h, the mixture was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate (3X). The combined organic phases were washed with brine, and dried

over anhydrous magnesium sulfate. Concentration gave 25 mg of the title compound as a viscous oil.
ESI-MS 274 (M+1-t-Bu); HPLC A: 3.09 min.

Step G: 4-(2-Ethylindazol-3-yl)piperidine, TFA salt

Using essentially the same method as Procedure 27, Step B, the title compound was obtained as the TFA salt

PROCEDURE 45

4-(1,3-Diethyl-4-methyl-(1H)-pyrazol-5-yl)piperidine di-HCl salt

Step A: 1-(t-Butoxycarbonyl)-*4-(N*-methyl-*N*-methoxycarboxamido)piperidine

A solution of 1-(t-butoxycarbonyl)isonipecotic acid (13.74 g, 0.06 mol), TEA (14.7 mL, 0.105 mol), 4-DMAP (1.83 g, 0.015 mol), *N*-ethyl-*N*'-(3-dimethylaminopropyl)carbodiimide x HCl (11.50 g, 0.06 mol) and *O,N*-dimethylhydroxylamine x HCl (6.27 g, 0.09 mol) in methylene chloride (250 mL) was stirred at rt for 60 h. The mixture was partitioned between 1 L of ether and 500 mL of water and the layers were separated. The organic layer was washed with 500 mL of 1.0 N HCl, 500 mL of 1.0 N NaOH, 500 mL of sat'd sodium chloride, dried over magnesium sulfate and concentrated to afford 14.34 g (88%) of the title compound: ^{1}H NMR (500 MHz) δ 1.46 (s, 9H), 1.65-1.80 (4H), 2.76-2.86 (3H), 3.19 (s, 3H), 3.71 (s, 3H), 4.15 (2H).

Step B: 1-(t-Butoxycarbonyl)-4-formylpiperidine

A solution of 1-(t-butoxycarbonyl)-*4-(N*-methyl-*N*-methoxycarboxamido)piperidine (4.80 g, 17.6 mmol) (from Step A) in methylene chloride (100 mL) at –78 °C was treated with 1.0 M DIBALH solution in methylene chloride (25 mL) and stirred cold for 30 min. The reaction was quenched with 1.0 N HCl (250 mL) and warmed to rt. The quenched mixture was extracted with 300 mL of ether; the extract was washed with 150 mL of 1.0 N NaOH, 150 mL of sat'd sodium chloride, dried over magnesium sulfate and concentrated. Flash chromatography on 125 g of silica gel using 1:1 v/v hexanes/ether as the eluant afforded 3.60 g (95%) of the title compound:

^{1}H NMR (500 MHz) δ 1.46 (s, 9H), 1.52-1.59 (m, 2H), 1.85-1.91 (m, 2H), 2.38-2.43 (m, 1H), 2.93 (app t, J= 11.0, 2H), 3.95-4.05 (m, 2H), 9.66 (s, 1H).

Step C: 1-(t-Butoxycarbonyl)-4-(1-(RS)-hydroxy-2-(RS)-methyl-3-oxopent-1-yl)piperidine

A solution of diisopropylamine (0.63 mL, 4.5 mmol) in THF (16 mL) at 0 °C was treated with 1.6 M n-butyllithium in sol'n in hexanes (2.8 mL). The resulting solution was stirred at 0 °C for 10 min, then cooled to –78 °C. 3-Pentanone (0.41 mL, 4.1 mmol) was added and the resulting mixture was stirred cold for 1 h. A solution of 1-(t-butoxycarbonyl)-4-formylpiperidine (435 mg, 2.05 mmol) (from Step B) in THF (3 mL) was then added. After 15 min, the reaction was quenched with sat'd ammonium chloride (25 mL) and extracted with ether (100 mL). The extract was dried over magnesium sulfate and concentrated. MPLC (Biotage) on a 40S silica cartridge using 4:1 v/v, then 3:2 v/v hexanes/ethyl acetate as the eluent afforded 517 mg (85%) of the title compound.

Step D: 1-(t-Butoxycarbonyl)-4-(1,3-dioxo-2-(RS)-methylpent-1-yl)piperidine

A solution of oxalyl chloride (0.34 mL, 3.9 mmol) in methylene chloride (12 mL) at –78 °C was treated with DMSO (0.43 mL, 6.0 mmol) and the resulting mixture was stirred cold for 10 min. A solution of 1-(t-butoxycarbonyl)-4-(1-(RS)-hydroxy-2-(RS)-methyl-3-oxopent-1-yl)piperidine (514 mg, 1.7 mmol) (from Step C) was added and the resulting solution was stirred cold for 1 h. N,N-Diisopropylethylamine (2.4 mL, 13.7 mmol) was added and the resulting mixture was warmed to 0 °C. The reaction was quenched with 1.0 N HCl (25 mL) and extracted with ether (100 mL). The extract was dried over magnesium sulfate and concentrated. MPLC (Biotage) on a 40S silica cartridge using 2:1 v/v hexanes/ethyl acetate as the eluent afforded 435 mg (85%) of the title compound.

Step E: 1-(t-Butoxycarbonyl)-4-(1,3-diethyl-4-methyl-(1H)-pyrazol-5-yl)piperidine

A solution of 1-(t-butoxycarbonyl)-4-(1,3-dioxo-2-(RS)-methylpent-1-yl)piperidine (435 mg, 1.5 mmol) (from Step D) in 2:1 v/v acetonitrile/water (12 mL) was treated with ethylhydrazine (34% sol'n in water, 0.28 mL, 1.6 mmol) and the resulting mixture was stirred at rt for 20 h. The reaction mixture was partitioned between 75 mL of ether and 25 mL of sat'd sodium chloride and the layers were separated. The organic layer was dried over magnesium sulfate and concentrated. MPLC (Biotage) on a 40S silica cartridge using 4:1 v/v, then 1:1 v/v hexanes/ethyl acetate as the eluent afforded 348 mg (74%) of the title compound:
^{1}H NMR (500 MHz) δ 1.21 (t, J= 7.5, 3H), 1.36 (t, J= 7.5, 3H), 1.49 (s, 9H), 1.68-1.72 (m, 2H), 1.86-1.91 (m, 2H), 2.54 (q, J= 1.5, 2H), 2.72-2.79 (3H), 4.08 (q, J= 7.5, 2H), 4.20-4.30 (m, 2H).

Step F: 4-(1,3-Diethyl-4-methyl-(1H)-pyrazol-5-yl)piperidine di-HCl salt

A solution of 1-(t-butoxycarbonyl)-4-(1,3-diethyl-4-methyl-(1H)-pyrazol-5-yl)piperidine (348 mg) (from Step E) in 2.5 N HCl in methanol was stirred at rt for 16 h. The solution was concentrated and the resulting solid was suspended in ethyl acetate, filtered and dried to afford 293 mg (92%) of the title compound.

PROCEDURE 46

Using essentially the same methods as described in Procedure 45 and substituting the appropriate starting material and/or hydrazine reagent, a variety of other 4-(1,3,4-trialkyl)-(1H)-pyrazol-5-yl)piperidines can be prepared, usually as the di-hydrochloride salts, and utilized in the following Examples as required.

PROCEDURE 47

Using essentially the same methods as described in Procedures 1 and 2 and substituting the appropriate starting material and/or hydrazine reagent, the following representative 4-(3-(substituted)-1-(H or alkyl)-(1H)-pyrazol-5-yl)piperidines can be prepared, usually as the di-hydrochloride salts, and utilized in the following Examples as required.

4-(3-(Benzyl)-1-(methyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(Benzyl)-1-(n-propyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(Benzyl)-1-(isopropyl)-(1H)-pyrazol-5-yl)piperidine

4-(3-(2-Fluorobenzyl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(3-Fluorobenzyl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(4-Fluorobenzyl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(4-Fluorobenzyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(4-Fluorobenzyl)-1-(methyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(4-Fluorobenzyl)-1-(n-propyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(3,4-Difluorobenzyl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(3,4-Difluorobenzyl)-1-(methyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(3,4-Difluorobenzyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(3,5-Difluorobenzyl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(2,4-Difluorobenzyl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(3-Chlorobenzyl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(4-Chlorobenzyl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(3,4-Dichlorobenzyl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(3-Cyanobenzyl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(4-Cyanobenzyl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(3-Methylsulfonylbenzyl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(4-Methylsulfonylbenzyl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(3-Methoxybenzyl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(4-Methoxybenzyl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(4-Methoxybenzyl)-1-(methyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(4-Methoxybenzyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(3-Ethoxybenzyl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(4-Ethoxybenzyl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(4-Ethoxybenzyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(3-Isopropoxybenzyl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(4-Isopropoxybenzyl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(4-Cyclopropoxybenzyl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(4-Butoxybenzyl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(4-t-Butoxybenzyl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(4-Cyclobutoxybenzyl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(4-Difluoromethoxybenzyl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(4-Trifluoromethoxybenzyl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(4-(2,2,2-Trifluoroethoxy)benzyl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(3,4-Methylenedioxybenzyl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine

4-(3-(3,4-Dimethoxybenzyl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(3,4-Diethoxybenzyl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(3-Fluoro-4-methoxybenzyl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(4-Fluoro-3-methoxybenzyl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(3-Fluoro-4-ethoxybenzyl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(4-Fluoro-3-ethoxybenzyl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(3-Cyano-4-methoxybenzyl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(4-Cyano-3-methoxybenzyl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(3-Cyano-4-ethoxybenzyl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(4-Cyano-3-ethoxybenzyl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(Benzofuran-6-yl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(Benzofuran-5-yl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(2,3-Dihydrobenzofuran-6-yl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(4-Benzyloxybenzyl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(4-Hydroxybenzyl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(3-Methylbenzyl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(4-Methylbenzyl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(3-Ethylbenzyl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(4-Ethylbenzyl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(4-Ethylbenzyl)-1-(methyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(4-Ethylbenzyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(4-Isopropylbenzyl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(4-t-Butylbenzyl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(4-Trifluoromethylbenzyl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(3-Phenylbenzyl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(4-Phenylbenzyl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(1-Naphthyl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(2-Naphthyl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(4-Acetylbenzyl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(4-(1-Methyl-1-hydroxyethylbenzyl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(3-Trifluoromethylbenzyl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(4-Trifluoromethylbenzyl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(Pyridin-3-yl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(Pyridin-3-yl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(Cyclohexylmethyl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine

4-(3-(4-Methylcyclohexylmethyl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(Cycloheptylmethyl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(Pyran-4-ylmethyl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine
4-(3-(Thiopyran-4-ylmethyl)-1-(ethyl)-(1H)-pyrazol-5-yl)piperidine, S,S-dioxide

PROCEDURE 48

Using essentially the same methods as described in Procedures 22 - 26 and substituting the appropriate starting material and/or reagent, the following representative 4-(2-(substituted)-4-(H or alkyl)thiazol-5-yl)piperidines can be prepared, usually as the di-hydrochloride salts, and utilized in the following Examples as required.

4-(2-(Benzyl)-4-(ethyl)thiazol-5-yl)piperidine
4-(2-(Benzyl)-4-(methyl)thiazol-5-yl)piperidine
4-(2-(Benzyl)thiazol-5-yl)piperidine
4-(2-(2-Fluorobenzyl)-4-(ethyl)thiazol-5-yl)piperidine
4-(2-(2-Fluorobenzyl)-4-(methyl)thiazol-5-yl)piperidine
4-(2-(2-Fluorobenzyl)thiazol-5-yl)piperidine
4-(2-(3-Fluorobenzyl)-4-(ethyl)thiazol-5-yl)piperidine
4-(2-(3-Fluorobenzyl)-4-(methyl)thiazol-5-yl)piperidine
4-(2-(3-Fluorobenzyl)thiazol-5-yl)piperidine
4-(2-(4-Fluorobenzyl)-4-(ethyl)thiazol-5-yl)piperidine
4-(2-(4-Fluorobenzyl)-4-(methyl)thiazol-5-yl)piperidine
4-(2-(4-Fluorobenzyl)thiazol-5-yl)piperidine
4-(2-(2-Chlorobenzyl)-4-(ethyl)thiazol-5-yl)piperidine
4-(2-(2-Chlorobenzyl)-4-(methyl)thiazol-5-yl)piperidine
4-(2-(2-Chlorobenzyl)thiazol-5-yl)piperidine
4-(2-(3-Chlorobenzyl)-4-(ethyl)thiazol-5-yl)piperidine
4-(2-(3-Chlorobenzyl)-4-(methyl)thiazol-5-yl)piperidine
4-(2-(3-Chlorobenzyl)thiazol-5-yl)piperidine
4-(2-(4-Chlorobenzyl)-4-(ethyl)thiazol-5-yl)piperidine
4-(2-(4-Chlorobenzyl)-4-(methyl)thiazol-5-yl)piperidine
4-(2-(4-Chlorobenzyl)thiazol-5-yl)piperidine
4-(2-(3-Cyanobenzyl)-4-(ethyl)thiazol-5-yl)piperidine
4-(2-(3-Cyanobenzyl)-4-(methyl)thiazol-5-yl)piperidine

4-(2-(3-Cyanobenzyl)thiazol-5-yl)piperidine
4-(2-(4-Cyanobenzyl)-4-(ethyl)thiazol-5-yl)piperidine
4-(2-(4-Cyanobenzyl)-4-(methyl)thiazol-5-yl)piperidine
4-(2-(4-Cyanobenzyl)thiazol-5-yl)piperidine
4-(2-(3,4-Difluorobenzyl)-4-(ethyl)thiazol-5-yl)piperidine
4-(2-(3,4-Difluorobenzyl)-4-(methyl)thiazol-5-yl)piperidine
4-(2-(3,4-Difluorobenzyl)thiazol-5-yl)piperidine
4-(2-(3,5-Difluorobenzyl)-4-(ethyl)thiazol-5-yl)piperidine
4-(2-(3,5-Difluorobenzyl)-4-(methyl)thiazol-5-yl)piperidine
4-(2-(3,5-Difluorobenzyl)thiazol-5-yl)piperidine
4-(2-(2,4-Difluorobenzyl)-4-(ethyl)thiazol-5-yl)piperidine
4-(2-(2,4-Difluorobenzyl)-4-(methyl)thiazol-5-yl)piperidine
4-(2-(2,4-Difluorobenzyl)thiazol-5-yl)piperidine
4-(2-(3,4-Dichlorobenzyl)-4-(ethyl)thiazol-5-yl)piperidine
4-(2-(3,4-Dichlorobenzyl)-4-(methyl)thiazol-5-yl)piperidine
4-(2-(3,4-Dichlorobenzyl)thiazol-5-yl)piperidine
4-(2-(3,5-Dichlorobenzyl)-4-(ethyl)thiazol-5-yl)piperidine
4-(2-(3,5-Dichlorobenzyl)-4-(methyl)thiazol-5-yl)piperidine
4-(2-(3,5-Dichlorobenzyl)thiazol-5-yl)piperidine
4-(2-(2,4-Dichlorobenzyl)-4-(ethyl)thiazol-5-yl)piperidine
4-(2-(2,4-Dichlorobenzyl)-4-(methyl)thiazol-5-yl)piperidine
4-(2-(2,4-Dichlorobenzyl)thiazol-5-yl)piperidine
4-(2-(3-Methylbenzyl)-4-(ethyl)thiazol-5-yl)piperidine
4-(2-(3-Methylbenzyl)-4-(methyl)thiazol-5-yl)piperidine
4-(2-(3-Methylbenzyl)thiazol-5-yl)piperidine
4-(2-(4-Methylbenzyl)-4-(ethyl)thiazol-5-yl)piperidine
4-(2-(4-Methylbenzyl)-4-(methyl)thiazol-5-yl)piperidine
4-(2-(4-Methylbenzyl)thiazol-5-yl)piperidine
4-(2-(3-Ethylbenzyl)-4-(ethyl)thiazol-5-yl)piperidine
4-(2-(3-Ethylbenzyl)-4-(methyl)thiazol-5-yl)piperidine
4-(2-(3-Ethylbenzyl)thiazol-5-yl)piperidine
4-(2-(4-Ethylbenzyl)-4-(ethyl)thiazol-5-yl)piperidine
4-(2-(4-Ethylbenzyl)-4-(methyl)thiazol-5-yl)piperidine
4-(2-(4-Ethylbenzyl)thiazol-5-yl)piperidine
4-(2-(4-Isopropylbenzyl)-4-(ethyl)thiazol-5-yl)piperidine

4-(2-(4-Isopropylbenzyl)-4-(methyl)thiazol-5-yl)piperidine
4-(2-(4-Isopropylbenzyl)thiazol-5-yl)piperidine
4-(2-(4-t-Butylbenzyl)-4-(ethyl)thiazol-5-yl)piperidine
4-(2-(4-t-Butylbenzyl)-4-(methyl)thiazol-5-yl)piperidine
4-(2-(4-t-Butylbenzyl)thiazol-5-yl)piperidine
4-(2-(3-Trifluoromethylbenzyl)-4-(ethyl)thiazol-5-yl)piperidine
4-(2-(3-Trifluoromethylbenzyl)-4-(methyl)thiazol-5-yl)piperidine
4-(2-(3-Trifluoromethylbenzyl)thiazol-5-yl)piperidine
4-(2-(4-Trifluoromethylbenzyl)-4-(ethyl)thiazol-5-yl)piperidine
4-(2-(4-Trifluoromethylbenzyl)-4-(methyl)thiazol-5-yl)piperidine
4-(2-(4-Trifluoromethylbenzyl)thiazol-5-yl)piperidine
4-(2-(3-Methoxybenzyl)-4-(ethyl)thiazol-5-yl)piperidine
4-(2-(3-Methoxybenzyl)-4-(methyl)thiazol-5-yl)piperidine
4-(2-(3-Methoxybenzyl)thiazol-5-yl)piperidine
4-(2-(4-Methoxybenzyl)-4-(ethyl)thiazol-5-yl)piperidine
4-(2-(4-Methoxybenzyl)-4-(methyl)thiazol-5-yl)piperidine
4-(2-(4-Methoxybenzyl)thiazol-5-yl)piperidine
4-(2-(3-Ethoxybenzyl)-4-(ethyl)thiazol-5-yl)piperidine
4-(2-(3-Ethoxybenzyl)-4-(methyl)thiazol-5-yl)piperidine
4-(2-(3-Ethoxybenzyl)thiazol-5-yl)piperidine
4-(2-(4-Ethoxybenzyl)-4-(ethyl)thiazol-5-yl)piperidine
4-(2-(4-Ethoxybenzyl)-4-(methyl)thiazol-5-yl)piperidine
4-(2-(4-Ethoxybenzyl)thiazol-5-yl)piperidine
4-(2-(3-Trifluoromethoxybenzyl)-4-(ethyl)thiazol-5-yl)piperidine
4-(2-(3-Trifluoromethoxybenzyl)-4-(methyl)thiazol-5-yl)piperidine
4-(2-(3-Trifluoromethoxybenzyl)thiazol-5-yl)piperidine
4-(2-(4-Trifluoromethoxybenzyl)-4-(ethyl)thiazol-5-yl)piperidine
4-(2-(4-Trifluoromethoxybenzyl)-4-(methyl)thiazol-5-yl)piperidine
4-(2-(4-Trifluoromethoxybenzyl)thiazol-5-yl)piperidine
4-(2-(4-Methylsulfonylbenzyl)-4-(ethyl)thiazol-5-yl)piperidine
4-(2-(4-Methylsulfonylbenzyl)-4-(methyl)thiazol-5-yl)piperidine
4-(2-(4-Methylsulfonylbenzyl)thiazol-5-yl)piperidine
4-(2-(4-Nitrobenzyl)-4-(ethyl)thiazol-5-yl)piperidine
4-(2-(4-Nitrobenzyl)-4-(methyl)thiazol-5-yl)piperidine
4-(2-(4-Nitrobenzyl)thiazol-5-yl)piperidine

EXAMPLE 1

2-(RS or SR)-(1-(RS or SR)-3-(SR)-((4-(3-(phenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)-4-methylpentanoic acid hydrochloride salt and 2-(RS or SR)-(1-(SR or RS)-3-(SR)-((4-(3-(phenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)-4-methylpentanoic acid hydrochloride salt

Step A: Methyl (+-)-*trans*-4-methylene-2-phenylcyclopentanoate

A mixture of methyl *trans*-cinnamate (5.0 g, 31 mmol), tetrakis(triphenylphosphine) palladium(0) (2.6 g, 2.3 mmol), 1,2-bis(diphenylphosphino)ethane (0.70 g, 1.8 mmol) and 2-((trimethylsilyl)methyl)-2-propen-1-yl acetate (6.90 g, 37 mmol) in THF (60 mL) under argon was heated to reflux for 4 h. An additional aliquot of 2-((trimethylsilyl)methyl)-2-propen-1-yl acetate (3.40 g) was added and the reaction was continued for another 16 h. The volatiles were then removed *in vacuo* and the residue was purified by FC (10% ethyl acetate in hexanes) to afford the title compound (6.2 g).

^{1}H NMR ($CDCl_3$) δ: 2.52 (m, 1 H), 2.68 (m, 1 H), 2.75-2.9 (m, 2 H), 2.95 (ddd, 1 H), 3.45 (ddd, 1 H), 3.57 (s, 3 H), 4.92 (m, 2 H), 7.15-7.3 (m, 5 H).

Step B: (+-)-*trans*-1-Hydroxymethyl-4-methylene-2-phenylcyclopentane

Method A:

To a solution of methyl (+-)-*trans*-4-methylene-2-phenylcyclopentanoate (5.0 g, 23 mmol) from Step A in THF (30 mL) under nitrogen was added dropwise over 10 min 1M lithium aluminum hydride (LAH) in THF (23 mL). After 2 h at rt, the excess LAH was quenched by dropwise addition of ethyl acetate and the reaction was then poured into dilute aq. HCl. The mixture was extracted twice with ether and the organic layers were washed with brine, dried over sodium sulfate, combined and concentrated. The residue was purified by FC (20 - 30% ethyl acetate in hexanes) to afford the title product (4.5 g) as a white solid.

^{1}H NMR ($CDCl_3$) δ: 2.22 (m, 1 H), 2.33 (tq, 1 H), 2.48 (tq, 1 H), 2.62 (br ddq, 1 H), 2.76 (br ddq, 1 H), 2.91 (ddd, 1 H), 3.55 (dABq, 2 H), 4.87 (m, 2 H), 7.15-7.3 (m, 5 H).

Method B:

Step B1: (+-)-*trans*-4-Methylene-2-phenylcyclopentanoic acid

To a solution of methyl (+-)-*trans*-4-methylene-2-phenylcyclopentanoate prepared as in Step A (28.4 g, 131 mmol) in methanol (400 mL) was added 5N sodium hydroxide (131 mL, 656 mmol). The reaction was heated at 65 °C for 1 h then cooled and concentrated. The residue was diluted with water, acidified with 2M hydrochloric acid and extracted twice with methylene chloride. The organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated *in vacuo* to give the crude title acid (27.2 g) which was used directly in Step B.

Step B2: (+-)-*trans*-1-Hydroxymethyl-4-methylene-2-phenylcyclopentane

To a solution of (+-)-*trans*-4-methylene-2-phenylcyclopentanoic acid (26 g, 129 mmol) from Step B1 in THF (600 mL) under nitrogen at -10 °C was added dropwise over 15 min 1M lithium aluminum hydride (LAH) in THF (193 mL, 193 mmol). After 16 h at rt, the excess LAH was quenched by dropwise addition of acetone and the reaction was then poured into dilute aq. HCl. The mixture was extracted twice with ether and the organic layers were washed with brine, dried over sodium sulfate, combined and concentrated. The residue was purified by FC (20% ethyl acetate in hexanes) to afford the title product (23.8 g) which was the same as in Method A.

Step C: (+-)-*trans* -3-Hydroxymethyl-4-phenylcyclopentan-1-one

Into a solution of (+-)-*trans*-1-hydroxymethyl-4-methylene-2-phenylcyclopentane from Step B (22.7 g, 121 mmol) in methanol (200 mL) cooled in a dry ice/acetone bath was bubbled ozone until the blue color persisted. The excess ozone was removed with a stream of nitrogen and then dimethylsulfide (20 mL) was added. After 10 min, the bath was removed and the reaction was allowed to warm to rt over 16 h. The volatiles were removed *in vacuo* and the residue was purified by FC (15 -30% ethyl acetate in hexanes) to give the title compound (22.1 g).
^{1}H NMR ($CDCl_3$) δ: 2.2-2.5 (m, 4 H), 2.71 (dd, 1 H), 3.28 (m, 1 H), 3.65 (dABq, 2 H), 7.2-7.4 (m, 5 H).

Step D: (+-)-*trans* -3-t-Butyldimethylsilyloxymethyl-4-phenylcyclopentan-1-one

Method A:

To a solution of (+-)-*trans*-3-hydroxymethyl-4-phenylcyclopentan-1-one from Step C (5.0 g, 24 mmol) in methylene chloride (100 mL) was added t-butyldimethylsilyl chloride (11.5 g, 48 mmol) and DIPEA (8.6 mL, 48 mmol). The reaction mixture was stirred at rt for 16 h, poured into dilute aq. HCl and extracted twice with ether. The organic layers were washed with brine, dried over sodium sulfate, combined and concentrated. The residue was purified by FC (5% ethyl acetate in hexanes) to afford the title compound (6.5 g) as a oil.
^{1}H NMR ($CDCl_3$) δ: -0.01 and -0.03 (2 s, 6 H), 0.86 (s, 9 H), 2.2-2.5 (m, 4 H), 2.71 (dd, 1 H), 3.28 (m, 1 H), 3.55 (dABq, 2 H), 7.23 (m, 3 H), 7.34 (m, 2 H).

Method B:

Step B1: (+-)-*trans* -1-t-Butyldimethylsilyloxymethyl-4-methylene-2-phenylcyclopentane

To a solution of (+-)-*trans*-1-hydroxymethyl-4-methylene-2-phenylcyclopentane from Step B (2.5 g, 13.3 mmol) in methylene chloride (50 mL) was added t-butyldimethylsilyl chloride (3.0 g, 20 mmol) and DIPEA (4.7 mL, 27 mmol). The reaction mixture was stirred at rt for 16 h, poured into dilute aqueous HCl and extracted twice with ether. The organic layers were washed with brine, dried over sodium sulfate, combined and concentrated. The residue was purified by FC (5% ethyl acetate in hexanes) to afford the title product (4.2 g) as a oil.
^{1}H NMR ($CDCl_3$) δ: -0.04 and -0.05 (2 s, 6 H), 0.85 (s, 9 H), 2.22 (m, 1 H), 2.33 (tq, 1 H), 2.48 (tq, 1 H), 2.62 (br ddq, 1 H), 2.76 (br ddq, 1 H), 2.91 (ddd, 1 H), 3.45 (dABq, 2 H), 4.87 (m, 2 H), 7.15-7.3 (m, 5 H).

Step B2: (+-)-*trans*-1-t-Butyldimethylsilyloxymethyl-4-oxo-2-phenylcyclopentane

Into a solution of (+-)-*trans*-1-t-butyldimethylsilyloxymethyl-4-methylene-2-phenylcyclopentane from Step B1 (2.2 g, 7.3 mmol) in methanol (100 mL) cooled in a dry ice/acetone bath was bubbled ozone until the blue color persisted. The excess ozone was removed with a stream of nitrogen and then dimethylsulfide (5 mL) was added. After 10 min, the bath was removed and the reaction was allowed to warm to rt over 2 h. The volatiles were removed *in vacuo* and the residue was purified by FC (15 -30% ethyl acetate in hexanes) to give the title compound (1.9 g) which was the same as in Method A.

Step E: Ethyl (E and Z)-3-(SR)-t-butyldimethylsilyloxymethyl-4-(SR)phenylcyclopent-1-ylideneacetate

To a solution of 60% sodium hydride in mineral oil (0.091g, 2.3 mmol) in THF (1 mL) was added triethyl phosphonoacetate (0.564 mL, 0.637 g, 2.8 mmol). The reaction mixture was stirred at rt for 30 min. To this solution was added a solution of (+-)-*trans*-3-t-butyldimethylsilyloxymethyl-4-phenylcyclopentan-1-one from Step D (0.173 g, 0.57 mmol) in THF (1 mL). The reaction mixture was stirred at rt for 2 days, diluted with chloroform, poured into water and extracted three times with chloroform. The organic layers were combined, washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by FC (10% ethyl acetate in hexanes) to afford the title compound as a 1 : 1 mixture of E : Z double bond isomers (0.193 g) as an oil.

^{1}H NMR ($CDCl_3$): δ -0.01(s, 3 H), -0.03 (s, 3 H), 0.86 (s, 9 H), 1.23 and 1.27 (2 t, 3 H), 2.15 - 2.26 (m, 1 H), 2.50 - 2.65 (m, 0.5 H), 2.65 - 2.74 (m, 1.5 H), 2.77 - 2.95 (m, 1 H), 2.95 -3.05 (m, 1 H), 3.17 - 3.26 (m, 0.5 H), 3.38 - 3.46 (m, 1.5 H), 3.54 - 3.61 (m, 1 H), 4.13 and 4.17 (2q, 2 H), 5.50 - 5.82 (m, 1 H), 7.15 - 7.24 (m, 3 H), 7.25 - 7.32 (m, 2H)

Step F: Ethyl (1-(RS and SR)-3-(SR)-hydroxymethyl-4-(SR)-phenylcyclopent-1-yl)acetate

A solution of ethyl (E and Z)-3-(SR)-t-butyldimethylsilyloxymethyl-4-(SR)phenylcyclopent-1-ylideneacetate from Step E in methanol (5 mL) was hydrogenated with 20% palladium hydroxide on carbon (0.040 g) at 45 psi for 12 h. The catalyst was filtered off and the volatiles removed *in vacuo* to give 0.128 g of residue. The residue was purified by FC (20% ethyl acetate in hexanes) to afford the title compound (0.099 g) as a 3 : 1 mixture of epimers at the C-1 position of the cyclopentyl.

^{1}H NMR ($CDCl_3$): δ 1.10 - 1.25 (m, 0.5 H), 1.23 (t, 3 H), 1.60 - 1.71 (m, 0.5 H), 1.74-1.88 (m, 1 H), 1.97 - 2.07 (m, 1 H), 2.13 - 2.30 (m, 2 H), 2.33 - 2.43 (m, 2.5 H), 2.55 - 2.67 (m, 0.5 H), 3.18 - 3.28 (m, 0.5 H), 3.84 (dd, 0.5 H), 3.42 - 3.52 (m, 1 H), 3.56 - 3.65 (m, 1 H), 4.10 (q, 2 H), 7.13 - 7.31 (m, 5 H)□□

Step G: Ethyl (1-(RS and SR)-3-(SR)-t-butyldimethylsilyloxymethyl-4-(SR)-phenylcyclopent-1-yl)acetate

To a solution of ethyl (1-(RS and SR)-3-(SR)-hydroxymethyl-4-(SR)-phenylcyclopent-1-yl)acetate from Step F (0.057 g, 0.22 mmol) in methylene chloride (5 mL) was added DIPEA (0.113 mL, 0.084 g, 0.65 mmol) and t-butyldimethylsilyl chloride (0.036 g, 0.24 mmol). The reaction mixture was stirred at rt for 12 h. TLC analysis indicated that the reaction was not complete. Additional DIPEA (0.226 mL, 0.17 g, 1.3 mmol) and t-butyldimethylsilyl chloride (0.072 g, 0.480) was added. The reaction mixture was stirred at rt for another 48 h, poured into aqueous sodium bicarbonate, and extracted three times with methylene chloride. The organic layers were combined, washed with brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by FC (5% ethyl acetate in hexanes) to afford the title product (0.074 g) as a oil.
MS/EI (80% MeOH/CH_2Cl_2): m/z 319 (M - t-butyl)

Step H: Ethyl 2-(RS and SR)-(1-(RS and SR)-3-(SR)-t-butyldimethylsilyloxymethyl-4-(SR)-phenylcyclopent-1-yl)-4-methylpent-4-enoate

To a solution of THF (5 mL) at -78 °C was added 1.5 M lithium diisopropylamide mono(tetrahydrofuran) solution in cyclohexane (0.662 mL, 0.99 mmol). To this solution was then added a solution of ethyl (1-(RS and SR)-3-(SR)-t-butyldimethylsilyloxymethyl-4-(SR)-phenylcyclopent-1-yl)acetate from Step G (0.280 g, 0.76 mmol) in THF (1 mL) and the reaction mixture was stirred at -78 °C for 1 h. To this solution was then added 3-bromo-2-methylprop-1-ene (0.235 mL, 0.309 g, 2.3 mmol). The reaction mixture was stirred for 1.5 h and allowed to warm to rt. The reaction mixture was then diluted with diethyl ether, poured into water and extracted three times with diethyl ether. The organic layers were combined, washed with brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by FC (3% ethyl acetate in hexanes) to afford the title product (0.256 g) as an oil.
^{1}H NMR ($CDCl_3$): δ -0.02, -0.03, -0.03 and -0.04 (4 s, 6 H), 0.86 and 0.84 (2 s, 9 H), 1.20 and 1.24 (2 t, 3 H), 1.12 - 1.26 (m, 0.5 H), 1.29 - 1.46 (m, 0.5 H), 1.53 - 1.70 (m, 0.5 H), 1.73 and 1.71 (2 s, 3 H), 1.84 - 2.09 (m, 2.5 H), 2.12 - 2.26 (m, 3 H), 2.32 - 2.52 (m, 3 H), 2.72 - 2.81 (m, 0.5 H), 2.83 - 2.89 (m, 0.5 H), 3.38 - 3.43 (m, 1 H), 3.51 - 3.57 (m, 1 H), 4.06 and 4.12 (2 q, 2 H), 4.69 - 4.72 (m, 1 H), 7.13 - 7.19 (m, 3 H), 7.21 - 7.28 (m, 2 H)

Step I: Ethyl 2-(RS or SR)-(1-(RS and SR)-3-(SR)-hydroxymethyl-4-(SR)-phenylcyclopent-1-yl)-4-methylpentanoate and ethyl 2-(SR or RS)-(1-(RS and SR)-3-(SR)-hydroxymethyl-4-(SR)-phenylcyclopent-1-yl)-4-methylpentanoate

A solution of ethyl 2-(RS and SR)-(1-(RS and SR)-3-(SR)-t-butyldimethylsilyloxymethyl-4-(SR)-phenylcyclopent-1-yl)-4-methylpent-4-enoate from Step H (0.116 g, 0.269 mmol) in ethanol (5 mL) was hydrogenated with 20% palladium hydroxide on carbon (0.030 g) at 45 psi for 5.5 h. The catalyst was filtered off using excess ethanol and 2-3 drops of concentrated HCl was added. After 12 h at rt, the volatiles were removed *in vacuo* to give 0.086 g of residue. The residue was purified by FC (5-20% ethyl acetate in hexanes) to afford separation at the 2-position of the substituted ethyl pentanoate to afford the higher R_f (0.035 g) and lower R_f (0.028 g) racemic title compounds as a mixture of two C-1 cyclopentyl diastereomers, but stereochemistries were not assigned.

(higher R_f): ^{1}H NMR ($CDCl_3$): δ 0.89 and 0.87 (2 d, 6 H), 1.13 - 1.20 (m, 0.5 H), 1.21 (t, 3 H), 1.24 - 1.30 (m, 0.5 H), 1.43 - 1.55 (m, 1 H), 1.56 - 1.69 (m, 2 H), 1.80 - 1.91 (m, 1.5 H), 1.91 - 2.04 (m, 0.5 H), 2.11 - 2.23 (m, 2.5 H), 2.28 - 2.40 (m, 2.5 H), 2.62 - 2.71 (m, 0.5 H), 2.78 (dd, 0.5 H), 3.45 - 3.47 (m, 1 H), 3.59 - 3.63 (m, 1 H), 4.05 - 4.13 (m, 2 H), 7.14 - 7.18 (m, 3 H), 7.21 - 7.29 (m, 2 H)

(lower R_f): ^{1}H NMR ($CDCl_3$): δ 0.86 (app t, 6 H), 1.18 -1.30 (m, 1 H), 1.26 (t, 3 H), 1.41 - 1.50 (m, 1 H), 1.55 - 1.68 (m, 1.5 H), 1.72 - 1.76 (m, 0.5 H), 1.79 - 1.87 (m, 0.5 H), 1.93- 2.04 (m, 1.5 H), 2.13 - 2.22 (m, 2.5 H), 2.23 - 2.37 (m, 2.5 H), 2.68 - 2.75 (m, 0.5 H), 2.77 - 2.84 (m, 0.5 H), 3.46 - 3.50 (m, 1 H), 3.55 - 3.62 (m, 1 H), 4.10 (q, 2 H), 7.14 - 7.22 (m, 3 H), 7.24 - 7.29 (m, 2 H)

Step J: Ethyl 2-(RS or SR)-(1-(RS and SR)-3-(SR)-formyl-4-(SR)-phenylcyclopent-1-yl)-4-methylpentanoate

To a solution of oxalyl chloride (0.026 mL, 0.038 g, 0.30 mmol) in methylene chloride (1 mL) at -70 °C was added dropwise DMSO (0.043 mL, 0.047 g, 0.60 mmol). After 10 min, a solution of the higher R_f isomer from Step I (0.032 g, 0.10 mmol) in methylene chloride (1 mL) was added dropwise. The reaction mixture was stirred at -70 °C for 45 min and then TEA (0.126 mL, 0.092 g, 0.90 mmol) was added. The reaction mixture was allowed to warm to rt for 10 min and then diluted with methylene chloride, poured into water, and extracted three times

with methylene chloride. The organic layers were combined, washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to afford the title compound (0.031 g) which was used directly in Step K.

Step K: Ethyl 2-(RS or SR)-(1-(RS and SR)-3-(SR)-((4-(3-(phenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)-4-methylpentanoate

To a solution of ethyl 2-(RS or SR)-(1-(RS and SR)-3-(SR)-formyl-4-(SR)-phenylcyclopent-1-yl)-4-methylpentanoate from Step J (0.011 g, 0.035 mmol) in 1,2-dichloroethane (0.5 mL) was added 4-(3-(phenyl)prop-1-yl) piperidine (0.011 g, 0.052 mmol) and acetic acid (0.003 mL, 0.003 g, 0.052 mmol). After 10 min, sodium triacetoxyborohydride (0.015 g, 0.069 mmol) was added and the reaction mixture was stirred at rt for 15 min. The reaction mixture was diluted with methylene chloride, poured into aqueous sodium bicarbonate and extracted three times with methylene chloride. The organic layers were combined, washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to afford 0.021 g. The residue was purified by prep TLC eluting with 2% MeOH in methylene chloride to afford the title compound (0.013 g) as a mixture of epimers at the C-1 position of the cyclopentyl. HPLC/MS (ESI): m/z 504 (M + 1).

Step L: 2-(RS or SR)-(1-(RS or SR)-3-(SR)-((4-(3-(Phenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)-4-methylpentanoic acid and 2-(RS or SR)-(1-(SR or RS)-3-(SR)-((4-(3-(phenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)-4-methylpentanoic acid

To a solution of ethyl 2-(RS or SR)-(1-(RS and SR)-3-(SR)- ((4-(3-(phenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)-4-methylpentanoate from Step K (0.013 g, 0.025 mmol) in MeOH (0.5 mL) was added 5.0M sodium hydroxide solution (0.075 mL, 0.375 mmol). The reaction mixture was stirred at 60 °C for 72 h. The reaction mixture was neutralized using 5% hydrochloric acid, diluted with methylene chloride, poured into water and extracted three times with methylene chloride. The organic layers were combined, washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by Prep TLC eluting with 84:14:1:1 methylene chloride/methanol/ammonium hydroxide/water to give separation at the cyclopentyl C-1 position of the two

diastereomeric racemic title products, higher R_f (0.0011 g) and lower R_f (0.0045 g). The stereochemistries for each were not assigned.

Step M: 2-(RS or SR)-(1-(RS or SR)-3-(SR)-((4-(3-(Phenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)-4-methylpentanoic acid hydrochloride salt and 2-(RS or SR)-(1-(SR or RS)-3-(SR)-((4-(3-(phenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)-4-methylpentanoic acid hydrochloride salt

The individual products from Step L were each taken up in 1:1 methylene chloride:ether (0.5 mL) and 1N hydrochloric acid in diethyl ether was added (0.007 mL, 0.007 mmol) to the higher R_f sample and (0.028 mL, 0.028 mmol) to the lower R_f sample. The volatiles were removed under a stream of nitrogen to give the title racemic compounds as a white solids.

HPLC/MS (ESI): m/z 476 (M + 1) (for each isomer).

EXAMPLE 2

2-(SR or RS)-(1-(RS or SR)-3-(SR)-((4-(3-(Phenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)-4-methylpentanoic acid hydrochloride salt and 2-(SR or RS)-(1-(SR or RS)-3-(SR)-((4-(3-(phenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)-4-methylpentanoic acid hydrochloride salt

Using essentially the same procedure as in Example 1, Steps J-M, the lower R_f isomer at the 2-position of the ethyl pentanoate from Example 1, Step I was elaborated to afford the two separate cyclopentyl C-1 title compounds, the higher R_f isomer (0.008 g) and the lower R_f isomer (0.0014 g). The stereochemistries for each were not assigned.

HPLC/MS (ESI): m/z 476 (M + 1) (for each isomer).

EXAMPLE 3

2-(RS or SR)-(1-(RS or SR)-3-(SR)-((4-(3-(Benzofurazan-5-yl)prop-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)cyclohexylacetic acid hydrochloride salt and 2-(RS or SR)-(1-(SR or RS)-3-(SR)-((4-(3-(benzofurazan-5-yl)prop-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)cyclohexylacetic acid hydrochloride salt

Step A: (1-(RS and SR)-3-(SR)-t-butyldimethylsilyloxymethyl-4-(SR)-phenylcyclopent-1-yl)acetic acid

To a solution of ethyl (1-(RS and SR)-3-(SR)-t-butyldimethylsilyloxymethyl-4-(SR)-phenylcyclopent-1-yl)acetate from Example 1, Step G (2.66 g, 7.06 mmol) in MeOH (70 mL) was added 2N sodium hydroxide solution (18 mL, 36 mmol). The reaction mixture was heated at 60 °C for 2 h, allowed to cool to rt, acidified with 18% citric acid until the pH = 4, diluted with methylene chloride, poured into water, and extracted three times with methylene chloride. The organic layers were combined, washed with brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by FC (30% ethyl acetate in hexanes with 0.5 % AcOH) to afford the title compound (2.15 g).

^{1}H NMR ($CDCl_3$): δ 0.00 (s, 6 H). 0.89 (s, 9H), 1.21 - 1.33 (m, 0.5 H), 1.43 - 1.52 (m, 0.5 H), 1.55 - 1.68 (m, 0.5 H), 1.75 - 1.88 (m, 0.5 H), 1.91 - 2.31 (m, 3 H), 2.38 - 2.50 (m, 2.5 H), 2.55 - 2.68 (m, 0.5), 2.78 -2.89 (m, 0.5 H), 2.90 - 2.99 (dd, 0.5 H), 3.45 (dd, 1 H), 3.52 - 3.60 (m, 1 H), 7.13 - 7.32 (m, 5 H).

Step B: 4-Methoxybenzyl (1-(RS and SR)-3-(SR)-t-**butyldimethylsilyloxymethyl-4-(SR)-phenylcyclopent-1-yl)acetate**

To a solution of (1-(RS and SR)-3-(SR)-t-butyldimethylsilyloxymethyl-4-(SR)-phenylcyclopent-1-yl)acetic acid from Step A (4.5 g, 13 mmol) in DMF (120 mL) was added triethylamine (2.3 mL, 1.7 g, 17 mmol) and 4-methoxybenzyl chloride (2.1 mL, 2.4 g, 15 mmol). The reaction mixture was stirred at rt for 12 h. TLC analysis showed only 10% conversion to the desired product. Additional triethylamine (4.6 mL, 3.4 g, 34 mmol) and 4-methoxybenzyl chloride (4.2 mL, 4.8 g, 30 mmol) were added. The reaction mixture was stirred at rt for an additional 48 h until TLC analysis indicated the reaction was complete. The reaction mixture was then diluted with diethyl ether, poured into saturated sodium bicarbonate, extracted three times with diethyl ether. The organic layers were combined, washed with brine, dried over sodium sulfate, filtered, and concentrated. The residue was purified by FC (3% ethyl acetate in hexane) to afford the title product (3.6 g).

^{1}H NMR ($CDCl_3$): δ -0.01 and 0.00 (2 s, 6 H), 0.88 (s, 9 H), 1.23 - 1.33 (m, 1 H), 1.42 - 1.49 (m, 0.5 H), 1.58 - 1.65 (m, 0.5 H), 1.77 - 1.83 (m, 0.5 H), 1.91 - 1.96 (m, 0.5 H), 2.03 (dt, 0.5 H), 2.10 - 2.27 (m, 1.5 H), 2.40 - 2.49 (m, 2.5 H), 2.58 - 2.66 (m,

0.5 H), 2.81 - 2.87 (m, 0.5 H), 2.91 (dd, 0.5 H), 3.44 (dd, 1 H), 3.54 - 3.58 (m, 1 H), 3.83 (s, 3 H), 5.08 (s, 2 H), 6.90 (d, 2 H), 7.17 - 7.28 (m, 3 H), 7.28 - 7.33 (m, 4 H).

Step C: 4-Methoxybenzyl 2-(RS and SR)-(1-(RS and SR)-3-(SR)-t-butyldimethylsilyloxymethyl-4-(SR)-phenylcyclopent-1-yl)cyclohex-2-en-1-ylacetate

To a solution of THF (5 mL) at -78 °C was added 1.5M lithium diisopropylamide mono(tetrahydrofuran) solution in cyclohexane (0.423 mL, 0.64 mmol). To this solution was then added a solution of 4-methoxybenzyl (1-(RS and SR)-3-(SR)-t-butyldimethylsilyloxymethyl-4-(SR)-phenylcyclopent-1-yl)acetate from Step B (0.229 g, 0.49 mmol) in THF (1.5 mL) and the reaction mixture was stirred at -78 °C for 1 h. To this solution was then added 3-bromocyclohexene (0.180 mL, 0.252 g, 1.6 mmol). The reaction mixture was stirred for 12 h as it was allowed to warm to rt and then diluted with diethyl ether, poured into saturated sodium bicarbonate and extracted three times with diethyl ether. The organic layers were combined, washed with brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by FC (1-3% ethyl acetate in hexanes) to afford the title product (0.123 g) as an oil.

^{1}H NMR ($CDCl_3$): δ -0.07, -0.06, -0.05, -0.04 and -0.03 (5 s, 6 H), 0.82 and 0.84 (2 s, 9 H), 1.14 - 1.27 (m, 0.5 H), 1.28 -1.42 (m, 1 H), 1.43 - 1.55 (m, 1 H), 1.66 - 1.83 (m, 3 H), 1.83 - 1.88 (m, 1 H), 1.90 - 2.03 (m, 3 H), 2.05 - 2.18 (m, 2 H), 2.28 - 2.38 (m, 0.5 H), 2.39 - 2.54 (m, 1.5 H), 2.55 - 2.70 (m, 0.5 H), 2.72 - 2.85 (m, 1 H), 3.33 - 3.42 (m, 1 H), 3.46 - 3.58 (m, 1 H), 3.77 and 3.79 (2 s, 3 H), 4.95 - 5.13 (m, 2 H), 5.58 - 5.72 (m, 2 H), 6.82 - 6.90 (m, 2 H), 7.10 - 7.18 (m, 3 H), 7.22 - 7.33 (m, 4 H).

Step D: 4-Methoxybenzyl 2-(RS and SR)-(1-(RS and SR)-3-(SR)-t-butyldimethylsilyloxymethyl-4-(SR)-phenylcyclopent-1-yl)cyclohexylacetate

A solution of 4-methoxybenzyl 2-(RS and SR)-(1-(RS and SR)-3-(SR)-t-butyldimethylsilyloxymethyl-4-(SR)-phenylcyclopent-1-yl) cyclohex-2-en-1-ylacetate from Step C (0.130 g, 0.24 mmol) in methanol (3 mL) was hydrogenated with palladium on carbon (0.027 g) at 45 psi for 15 min. The catalyst was filtered off and the volatiles removed *in vacuo* to give 0.130 g of a residue which was taken on to Step E without purification.

Step E: 4-Methoxybenzyl 2-(RS or SR)-(1-(RS and SR)-3-(SR)-hydroxymethyl-4-(SR)-phenylcyclopent-1-yl)cyclohexylacetate and 4-methoxybenzyl 2-(SR or RS)-(1-(RS and SR)-3-(SR)-hydroxymethyl-4-(SR)-phenylcyclopent-1-yl)cyclohexylacetate

To a solution of 4-methoxybenzyl 2-(RS and SR)-(1-(RS and SR)-3-(SR)-t-butyldimethylsilyloxymethyl-4-(SR)-phenylcyclopent-1-yl)cyclohexylacetate from Step D (0.130 g, 0.24 mmol) in THF (3 mL) was added a 1.0 M solution of tetrabutylammonium fluoride in THF (0.354 mL, 0.354 mmol) and the reaction mixture was stirred at rt for 12 h. The reaction mixture was diluted with ethyl acetate, poured into 5% aqueous HCl solution, extracted three times with ethyl acetate, combined organic layers, washed with brine, dried over sodium sulfate and concentrated to afford 0.088 g. The residue was purified by FC (3% ethyl acetate in methylene chloride) to afford separation at the 2-position of the cyclohexylacetate to give the higher R_f (0.030 g) and lower R_f (0.031 g) racemic title compounds as a mixture of the two possible cyclopentyl C-1 diastereomers, but stereochemistries were not assigned.

(higher R_f): ^{1}H NMR ($CDCl_3$): δ 0.93 -1.28 (m, 4 H), 1.47 (br s, 3 H), 1.52 - 1.75 (m, 5.5 H), 1.78 - 1.94 (m, 1.5 H), 1.96 - 2.02 (m, 0.5 H), 2.08 - 2.19 (m, 1.5 H), 2.22 - 2.28 (m, 1 H), 2.35 - 2.43 (m, 0.5 H), 2.56 - 2.71 (m, 1.5 H), 3.39 - 3.45 (m, 1 H), 3.54 - 3.60 (m, 1 H), 3.76 and 3.77 (2 s, 3 H), 5.01 and 5.02 (2 s, 2 H), 6.85 (d, 2 H), 7.12 - 7.19 (m, 3 H), 7.22 - 7.31 (m, 4 H).

(lower R_f): ^{1}H NMR ($CDCl_3$): δ 0.93 - 1.38 (m, 4 H), 1.47 (br s, 3 H), 1.52 - 1.72 (m, 5 H), 1.74 - 1.93 (m, 2 H), 1.95 - 2.03 (m, 0.5 H), 2.09 - 2.20 (m, 1.5 H), 2.22 - 2.28 (m, 1 H), 2.35 - 2.48 (m, 0.5 H), 2.53 - 2.60 (m, 0.5 H), 2.64 - 2.73 (m, 1 H), 3.39 - 3.45 (m, 1 H), 3.52 - 3.57 (m, 1 H), 3.79 (s, 3 H), 5.05 and 5.06 (2 s, 2 H), 6.87 (d, 2 H), 7.12 - 7.20 (m, 3 H), 7.23 - 7.31 (m, 4 H).

Step F: 4-Methoxybenzyl 2-(RS or SR)-(1-(RS and SR)-3-(SR)-formyl-4-(SR)-phenylcyclopent-1-yl)cyclohexylacetate

To a solution of oxalyl chloride (0.037 mL, 0.054 g, 0.42 mmol) in methylene chloride (1 mL) at -70 °C was added dropwise DMSO (0.060 mL, 0.066 g, 0.85 mmol). After 10 min, a solution of 4-methoxybenzyl 2-(RS or SR)-(1-(RS and SR)-3-(SR)-hydroxymethyl-4-(SR)-phenylcyclopent-1-yl)cyclohexylacetate the higher R_f isomer from Step E (0.030 g, 0.068 mmol) in methylene chloride (0.5 mL) was

added dropwise. The reaction mixture was stirred at -70 °C for 40 min and then triethylamine (0.177 mL, 0.128 g, 1.27 mmol) was added. The reaction mixture was allowed to warm to rt for 10 min and then diluted with methylene chloride, poured into water, and extracted three times with methylene chloride. The organic layers were combined, washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude title compound was used directly in Step G.

Step G: 4-Methoxybenzyl 2-(RS or SR)-(1-(RS and SR)-3-(SR)-((4-(3-(benzofurazan-5-yl)prop-1-yl)piperidin-1-yl)methyl-4-(SR)-phenylcyclopent-1-yl)cyclohexylacetate

To a solution of 4-methoxybenzyl 2-(RS or SR)-(1-(RS and SR)-3-(SR)-formyl-4-(SR)-phenylcyclopent-1-yl)cyclohexylacetate from Step F (0.027 g, 0.062 mmol) in 1,2-dichloroethane (2 mL) was added 4-(3-(benzofurazan-5-yl)prop-1-yl)piperidine hydrochloride (0.026 g, 0.093 mmol) and DIPEA (0.016 mL, 0.017 g, 0.093 mmol). After 10 min, sodium triacetoxyborohydride (0.026 g, 0.124 mmol) was added. The reaction mixture was stirred at rt for 12 h, diluted with methylene chloride, poured into aqueous sodium bicarbonate and extracted three times with methylene chloride. The organic layers were combined, washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by prep TLC eluting with 2% MeOH in methylene chloride to afford the title compound (0.018 g) as a mixture of epimers at the cyclopentyl C-1 position.
HPLC/MS (ESI): m/z 665 (M + 1).

Step H: 2-(RS or SR)-(1-(RS or SR)-3-(SR)-((4-(3-(Benzofurazan-5-yl)prop-1-yl)piperidin-1-yl)methyl-4-(SR)-phenylcyclopent-1-yl)cyclohexylacetic acid and 2-(RS or SR)-(1-(SR or RS)-3-(SR)-((4-(3-(benzofurazan-5-yl)prop-1-yl)piperidin-1-yl)methyl-4-(SR)-phenylcyclopent-1-yl)cyclohexylacetic acid

A solution of 4-methoxybenzyl 2-(RS or SR)-(1-(RS and SR)-3-(SR)-((4-(3-(benzofurazan-5-yl)prop-1-yl)piperidin-1-yl)methyl-4-(SR)-phenylcyclopent-1-yl)cyclohexylacetate from Step G (0.018 g, 0.027 mmol) was dissolved in 96% formic acid (1 mL) and stirred at rt for 12 h. The reaction mixture was neutralized using 5N NaOH, diluted with methylene chloride and extracted three times with methylene chloride. The organic layers were combined, washed with brine, dried over sodium sulfate and concentrated to afford 0.015 g. The residue was purified by prep TLC

eluting with 93:5:1:1 methylene chloride/methanol/ammonium hydroxide/water to give separation at the cyclopentyl C-1 position to afford the racemic title products, higher R_f (0.0022 g) and lower R_f (0.0047 g). The stereochemistries for each were not assigned.

Step I 2-(RS or SR)-(1-(RS or SR)-3-(SR)-((4-(3-(Benzofurazan-5-yl)prop-1-yl)piperidin-1-yl)methyl-4-(SR)-phenylcyclopent-1-yl)cyclohexylacetic acid hydrochloride salt and 2-(RS or SR)-(1-(SR or RS)-3-(SR)-((4-(3-(benzofurazan-5-yl)prop-1-yl)piperidin-1-yl)methyl-4-(SR)-phenylcyclopent-1-yl)cyclohexylacetic acid hydrochloride salt

The individual products from Step H were each taken up in 1:1 methylene chloride:ether (0.5 mL) and 1N hydrochloric acid in diethyl ether was added (0.012 mL, 0.012 mmol) to the higher R_f sample and (0.026 mL, 0.026 mmol) to the lower R_f sample. The volatiles were removed under a stream of nitrogen to give the title racemic compounds as a white solids.
HPLC/MS (ESI): m/z 544 (M + 1) (for each isomer).

EXAMPLE 4

2-(SR or RS)-(1-(RS or SR)-3-(SR)-((4-(3-(Benzofurazan-5-yl)prop-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)cyclohexylacetic acid hydrochloride salt and 2-(SR or RS)-(1-(SR or RS)-3-(SR)-((4-(3-(benzofurazan-5-yl)prop-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)cyclohexylacetic acid hydrochloride salt

Using essentially the same procedure as in Example 3, Steps F-I, the lower R_f isomer at the 2-position of the cyclohexylacetate from Example 3, Step E was elaborated to afford the two cyclopentyl C-1 title compounds, the higher R_f isomer (0.0027 g) and the lower R_f isomer (0.0042g). The stereochemistries for each were not assigned.
HPLC/MS (ESI): m/z 544 (M + 1) (for each isomer).

EXAMPLE 5

2-(RS or SR)-(1-(RS and SR)-3-(SR)-((4-(3-(4-Cyanophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)cyclohexylacetic acid hydrochloride salt

Using essentially the same procedure as in Example 3, Steps G-I, but substituting 4-(3-(4-cyanophenyl)prop-1-yl)piperidine hydrochloride in Step G, the title compound was obtained as a mixture of cyclopentyl C-1 diastereomers (0.014 g). In this case, separation of the two diastereomers was not achieved after Step H.
HPLC/MS (ESI): m/z 527 (M + 1).

EXAMPLE 6

2-(SR or RS)-(1-(RS and SR)-3-(SR)-((4-(3-(4-Cyanophenyl)prop-1-yl)piperidin-1-yl)methyl)- 4-(SR)-phenylcyclopent-1-yl)cyclohexylacetic acid hydrochloride salt

Using essentially the same procedure as in Example 4, Steps G-I, but substituting 4-(3-(phenyl)prop-1-yl)piperidine hydrochloride in Step G, the title compound was obtained as a mixture of cyclopentyl C-1 diastereomers (0.011 g). In this case, separation of the two diastereomers was not achieved after Step H.
HPLC/MS (ESI): m/z 527 (M + 1).

EXAMPLE 7

2-(RS or SR)-(1-(RS or SR)-3-(SR)-((4-(3-(Benzofurazan-5-yl)prop-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)-3-(cyclopropyl)propionic acid hydrochloride salt and 2-(RS or SR)-(1-(SR or RS)-3-(SR)-((4-(3-(benzofurazan-5-yl)prop-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)-3-(cyclopropyl)propionic acid hydrochloride salt

Using essentially the same procedure as in Example 3, Steps C and E-I, but substituting (bromomethyl)cyclopropane in Step C, the higher R_f isomer at the 2-position of the 3-(cyclopropyl)propionate from Step E was elaborated to give the two racemic cyclopentyl C-1 diastereomeric title compounds, the higher R_f isomer (0.002 g) and the lower R_f isomer (0.008 g). The stereochemistries for each were not assigned.
HPLC/MS (ESI): m/z 516 (M + 1) (for each isomer).

EXAMPLE 8

2-(SR or RS)-(1-(RS and SR)-3-(SR)-((4-(3-(Benzofurazan-5-yl)prop-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)-3-(cyclopropyl)propionic acid hydrochloride salt

Using essentially the same procedure as in Example 4, Steps C and E-I, but substituting (bromomethyl)cyclopropane in Step C, the lower R_f isomer at the 2-position of the 3-(cyclopropyl)propionate from Step E was elaborated to afford the title compound as a racemic mixture of the cyclopentyl C-1 diastereomers (0.0012 g). In this case, separation of the two diastereomers was not achieved after Step H.
HPLC/MS (ESI): m/z 516 (M + 1).

EXAMPLE 9

2-(RS or SR)-(1-(RS or SR)-3-(SR)-((4-(3-(Benzofurazan-5-yl)prop-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)-3-(cyclobutyl)propionic acid hydrochloride salt and 2-(SR or RS)-(1-(SR or RS)-3-(SR)-((4-(3-(benzofurazan-5-yl)prop-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)-3-(cyclobutyl)propionic acid hydrochloride salt

Using essentially the same procedure as in Example 3, Steps C and E-I, but substituting (bromomethyl)cyclobutane in Step C, the higher R_f isomer at the 2-position of the 3-(cyclobutyl)propionate from Step E was elaborated to give the two racemic cyclopentyl C-1 title compounds, the higher R_f isomer (0.0065 g) and the lower R_f isomer (0.014 g). The stereochemistries for each were not assigned.
HPLC/MS (ESI): m/z 531 (M + 1) (for each isomer).

EXAMPLE 10

2-(SR or RS)-(1-(RS and SR)-3-(SR)-((4-(3-(Benzofurazan-5-yl)prop-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)-3-(cyclobutyl)propionic acid hydrochloride salt

Using essentially the same procedure as in Example 4, Steps C and E-I, but substituting (bromomethyl)cyclobutane in Step C, the lower R_f isomer at the 2-position of the 3-(cyclobutyl)propionate from Step E was elaborated to afford the title compound as a mixture of the cyclopentyl C-1 diastereomers (0.013 g). In this case, separation of the two diastereomers was not achieved after Step H.
HPLC/MS (ESI): 531 m/z (M + 1).

EXAMPLE 11

2-(S or R)-(1-(R)-3-(S)-((4-(3-(4-Fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-3-(cyclopropyl)propionic acid hydrochloride salt (minor) and 2-(S or R)-(1-(S)-3-(S)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-3-(cyclopropyl)propionic acid hydrochloride salt (major)

Step A: (+-)-*trans*-4-Methylene-2-phenylcyclopentanoic acid

To a solution of methyl (+-)-*trans*-4-methylene-2-phenylcyclopentanoate prepared as in Example 1, Step A (28.4 g, 131 mmol) in methanol (400 mL) was added 5N sodium hydroxide (131 mL, 656 mmol). The reaction was heated at 65 °C for 1 h then cooled and concentrated. The residue was diluted with water, acidified with 2M hydrochloric acid and extracted twice with methylene chloride. The organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated *in vacuo* to give the crude title acid (27.2 g) which was used directly i Step B.

Step B: (+)-*trans*-4-Methylene-2-phenylcyclopentanoic acid, (S)-(-)- α -methylbenzylamine salt and (-)-*trans*-4-methylene-2-phenylcyclopentanoic acid, (R)-(+)- α -methylbenzylamine salt

The crude (+-)-*trans*-4-methylene-2-phenylcyclopentanoic acid from Step A (assumed 131 mmol) was taken up in 2-propanol (400 mL), warmed to 80 °C and treated with (S)-(-)- α -methylbenzylamine (8.45 mL, 66 mmol). The mixture was stirred while allowed to cool to rt over 16 h and was then cooled to -10 °C for 1 h. The salt was filtered, washed with a small amount of ether to remove 2-propanol and air dried to give 6.442 g of salt. This was recrystallized twice from 2-propanol to give the title salt (4.713 g), $[\alpha]_D = +56$ (MeOH, c = 0.20).

The combined mother liquors from above were concentrated and the residue was taken up in water, acidified with 2M hydrochloric acid and extracted twice with methylene chloride. The organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated *in vacuo*. The residue was taken up in 2-propanol (400 mL), warmed to 80 °C and treated with (R)-(+)- α -methylbenzylamine (9.1 mL, 70 mmol). The mixture was stirred while allowed to cool to rt over 16 h and was then cooled to -10 °C for 1 h. The salt was filtered, washed with a small amount of ether to remove 2-propanol and air dried to give 8.22 g of salt. This was recrystallized from 2-propanol to give the title salt (6.31 g), $[\alpha]_D = -55$ (MeOH, c = 0.21).

Step C: (+)-*trans*-4-Methylene-2-phenylcyclopentanoic acid and (-)-*trans*-4-methylene-2-phenylcyclopentanoic acid

Method A:

The (+)-*trans*-4-methylene-2-phenylcyclopentanoic acid, (S)-(-)- α -methylbenzylamine salt from Step B (4.7 g) was suspended in methylene chloride and water and acidified with 2M hydrochloric acid and extracted twice with methylene chloride. The organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated *in vacuo* to give the title (+) acid (3.1 g), $[\alpha]_D = +101$ (MeOH, c = 0.135).

Similarly, the (-)-*trans*-4-methylene-2-phenylcyclopentanoic acid, (R)-(+)- α -methylbenzylamine salt (6.3 g) was converted to the free (-)-title acid (4.23 g), $[\alpha]_D = -103$ (MeOH, c = 0.23).

Method B:

Step B1: 1-(S)-(((S)-(-)-4-Benzyl-2-oxazolidin-1-yl)carbonyl)-3-methylene-2-(S)-phenylcyclopentane (higher R_f) and 1-(R)-(((S)-(-)-4-benzyl-2-oxazolidin-1-yl)carbonyl)-3-methylene-2-(R)-phenylcyclopentane (lower R_f)

A solution of (+-)-*trans*-4-methylene-2-phenylcyclopentanoic acid (47.5 g, 235 mmol) in ether (1 L) and TEA (36 mL, 260 mmol) was cooled to -10 °C. Trimethylacetyl chloride (31.8 mL, 260 mmol) was then added slowly and after stirring at -10 °C for 10 min, the reaction was allowed to warm to 10 °C over 1 h. The reaction was then recooled to -60 °C.

To the above solution at -60 °C was added via a canula a solution of (S)-(-)-4-benzyl-2-oxazolidinone (45.8 g, 260 mmol) in THF (500 mL) which had been treated at -50 °C with 2.5 M n-butyl lithium (103 mL, 257 mmol) and aged at -50 °C for 45 min. The reaction was allowed to warm to rt over 16 h. The reaction was diluted with ether (1 L) and quenched with sat'd aqueous ammonium chloride (1 L). The layers were separated and the aqueous layer was reextracted with a second portion of ether. The organic layers were each washed twice with 2N hydrochloric acid, twice with 1N sodium hydroxide and brine, dried over sodium sulfate, combined and concentrated. The residue was purified by chromatography (20% ethyl acetate in

hexanes) to give the two diastereomeric products, higher R_f (18.4 g) and lower R_f (17.7 g).

Step B2: (+)-*trans*-4-Methylene-2-phenylcyclopentanoic acid

A solution of 1-(S)-(((S)-(-)-4-benzyl-2-oxazolidin-1-yl)carbonyl)-3-methylene-2-(S)-phenylcyclopentane (higher R_f product from Step B1) (20.9 g, 58 mmol) in a 3 : 1 mixture of THF : water (1 L) was cooled to 5 °C. Hydrogen peroxide (30%, 39.5 mL, 350 mmol) and lithium hydroxide (4.85 g, 106 mmol) were added and the reaction was stirred for 3.5 h. The excess peroxide was quenched by dropwise addition of sodium sulfite (60 g) in water (1 L) over 1.5 h while maintaining the temperature below 5 °C. After stirring for 2 additional h, most of the THF was removed *in vacuo* and the aqueous layer was washed 3 times with methylene chloride. The aqueous layer was acidified to pH = 2 with conc. HCl and reextracted twice with methylene chloride. The organic layers were washed with brine, dried and concentrated to give the (+) title product, $[\alpha]_D = +100.5$ (MeOH, c = 0.207).

Step D: (+)-*trans*-1-Hydroxymethyl-4-methylene-2-phenylcyclopentane and (-)-*trans*-1-hydroxymethyl-4-methylene-2-phenylcyclopentane

Method A:

A solution of (+)-*trans*-4-methylene-2-phenylcyclopentanoic acid from Step C (4.15 g, 20.5 mmol) in THF (100 mL) under nitrogen was cooled to -7 °C and 1M LAH in THF (31 mL, 31 mmol) was added dropwise over 15. The reaction was allowed to warm to rt over 16 h. The excess LAH was quenched by dropwise addition of acetone and the reaction was then poured into dilute aq. HCl. The mixture was extracted twice with ether and the organic layers were washed with brine, dried over sodium sulfate, combined and concentrated. The residue was purified by FC (20% ethyl acetate in hexanes) to afford the title (+) product (3.93 g), $[\alpha]_D = +50$ (MeOH, c = 0.20).

Similarly, the (-)-*trans*-4-methylene-2-phenylcyclopentanoic acid from Step C (4.23 g) was converted to the title (-) alcohol (3.75 g), $[\alpha]_D = -51$ (MeOH, c = 0.2).

Method B:

Prep-HPLC of (+-)-*trans*-4-methylene-2-phenylcyclopentanoic from Example 1, Step B using a Chiracel OD column (5-10% isopropanol in hexanes) affords good separation of the title (-) enantiomer as the first eluting band and the (+) enantiomer as the second eluting band.

Step E: (+)-*trans*-1-t-Butyldimethylsilyloxymethyl-4-methylene-2-phenylcyclopentane and (-)-*trans*-1-t-butyldimethylsilyloxymethyl-4-methylene-2-phenylcyclopentane

To a solution of (+)-*trans*-1-hydroxymethyl-4-methylene-2-phenylcyclopentane from Step D (3.9 g, 21 mmol) in methylene chloride (50 mL) was added t-butyldimethylsilyl chloride (4.7 g, 31 mmol) and DIPEA (7.3 mL, 42 mmol). The reaction was stirred at rt for 16 h, poured into dilute aq. HCl and extracted twice with ether. The organic layers were washed with brine, dried over sodium sulfate, combined and concentrated. The residue was purified by FC (100% hexanes) to afford the title product (5.6 g) as a oil, $[\alpha]_D = +42.3$ (MeOH, c = 0.18).

Similarly, (-)-*trans*-1-hydroxymethyl-4-methylene-2-phenylcyclopentane from Step D (3.75 g) was converted to the title (-) silylether (5.5 g), $[\alpha]_D = -44.4$ (MeOH, c = 0.18).

Step F: (+)-*trans*-3-Hydroxymethyl-4-phenylcyclopentan-1-one and (-)-*trans*-3-hydroxymethyl-4-phenylcyclopentan-1-one

Method A:

A solution of (+)-*trans*-1-t-butyldimethylsilyloxymethyl-4-methylene-2-phenylcyclopentane from Step E (4.6 g, 15 mmol) in methanol (100 mL) was cooled to -70 °C in a dry-ice acetone bath and ozone was bubbled through until a blue color persisted which was discharged with a stream of nitrogen. Dimethylsulfide (10 mL) was added and after 15 min, the reaction was allowed to warm to rt over 16 h. Since by TLC (20% ethyl acetate in hexanes) indicated that there was significant loss of the silyl as well as dimethylketal formation, the methanol was mostly remove *in vacuo*. The residue was diluted with water and treated with sulfuric acid (6 mL) and stirred for 2 h. The mixture was extracted twice with ethyl acetate and the organic layers were washed with brine (containing some sodium bicarbonate), dried over sodium sulfate, combined and concentrated. The residue was purified by FC (15 - 30% ethyl

acetate in hexanes) to give the (+) title ketone/alcohol (2.87 g), $[\alpha]_D = -96$ (MeOH, c = 0.2).

Similarly, (-)-*trans*-1-t-butyldimethylsilyloxymethyl-4-methylene-2-phenylcyclopentane from Step E (4.4 g) was converted to the title (-) ketone/alcohol (2.8 g), $[\alpha]_D = +97$ (MeOH, c = 0.2)..

Method B:

The title compounds can also be obtained directly from (+)-*trans*-1-hydroxymethyl-4-methylene-2-phenylcyclopentane and (-)-*trans*-1-hydroxymethyl-4-methylene-2-phenylcyclopentane by ozonolysis as above. Thus, (+)-*trans*-1-hydroxymethyl-4-methylene-2-phenylcyclopentane (3.7 gm, 20 mmol) afforded (+)-*trans*-1-hydroxymethyl-4-oxo-2-phenylcyclopentane (3.5 g).

Step G: (+)-*trans*-1-t-Butyldimethylsilyloxymethyl-4-oxo-2-phenylcyclopentane and (-)-*trans*-1-t-butyldimethylsilyloxymethyl-4-oxo-2-phenylcyclopentane

To a solution of (+)-*trans*-3-hydroxymethyl-4-phenylcyclopentan-1-one from Example 11, Step F (3.3 g, 16 mmol) in methylene chloride (100 mL) was added t-butyldimethylsilyl chloride (11 g, 49 mmol) and DIPEA (22 mL, 74 mmol). The reaction was stirred at rt for 16 h, poured into dilute aq. hydrochloric acid and extracted twice with ether. The organic layers were washed with brine, dried over sodium sulfate, combined and concentrated. The residue was purified by FC (5% ethyl acetate in hexanes) to afford of (+)-*trans*-1-t-butyldimethylsilyloxymethyl-4-oxo-2-phenylcyclopentane (6.3 g) as a oil.

Step H: Ethyl (E and Z)-3-(S)-t-butyldimethylsilyloxymethyl-4-(S)-phenylcyclopent-1-ylideneacetate

To a solution of 60% sodium hydride in mineral oil (1.2 g, 29 mmol) in THF (75 mL) was added triethyl phosphonoacetate (7.3 mL, 8.3 g, 37 mmol). The reaction mixture was stirred at rt for 30 min. To this solution was then added a solution of (+)-*trans*-3-t-butyldimethylsilyloxymethyl-4-phenylcyclopentan-1-one from Step G (3.95 g,13 mmol) in THF (5 mL). The reaction mixture was stirred at rt for 2 days, diluted with diethyl ether, poured into water and extracted three times with

diethyl ether. The organic layers were combined, washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by FC (1% ethyl acetate in hexanes) to afford the title compound as a 1 : 1 mixture of E : Z double bond isomers (5.12 g) as an oil.

^{1}H NMR ($CDCl_3$): δ -0.01(s, 3 H), -0.03 (s, 3 H), 0.86 (s, 9 H), 1.23 and 1.27 (2 t, 3 H), 2.15 - 2.26 (m, 1 H), 2.50 - 2.65 (m, 0.5 H), 2.65 - 2.74 (m, 1.5 H), 2.77 - 2.95 (m, 1 H), 2.95 - 3.05 (m, 1 H), 3.17 - 3.26 (m, 0.5 H), 3.38 - 3.46 (m, 1.5 H), 3.54 - 3.61 (m, 1 H), 4.13 and 4.17 (2 q, 2 H), 5.78 - 5.82 (m, 1 H), 7.15 - 7.24 (m, 3 H), 7.25 - 7.32 (m, 2 H)

Step I: Ethyl (1-(R and S)-3-(S)-t-butyldimethylsilyloxmethyl-4-(S)-phenylcyclopent-1-yl)acetate

A solution of ethyl (E and Z)-3-(S)-t-butyldimethylsilyloxymethyl-4-(S)-phenylcyclopent-1-ylideneacetate from Step H in ethanol (80 mL) was hydrogenated with palladium on carbon (0.560 g) at 45 psi for 4.5 h. The catalyst was filtered off and the volatiles removed *in vacuo* to give the title compound (4.80 g) as a 3 : 1 mixture of S : R epimers at the C-1 cyclopentyl which was taken onto Step J without purification.

Step J: (1-(R and S)-3-(S)-t-Butyldimethylsilyloxymethyl-4-(S)-phenylcyclopent-1-yl)acetic acid

To a solution of ethyl (1-(R and S)-3-(S)-t-butyldimethylsilyloxymethyl-4-(S)-phenylcyclopent-1-yl)acetate from Step I (4.80 g, 13 mmol) in MeOH (150 mL) was added 1 N sodium hydroxide solution (64 mL, 64 mmol). The reaction mixture was stirred at rt for 12 h. TLC analysis showed that the reaction was not complete so the reaction mixture then was heated to 60 °C for 20 min until all of the starting material was consumed. The reaction mixture was allowed to cool to rt, acidified with 18% citric acid until the pH = 4, diluted with methylene chloride, poured into water, and extracted three times with methylene chloride. The organic layers were combined, washed with brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by FC (30% ethyl acetate in hexanes with 0.5 % AcOH) to afford the title compound (4.45 g).

^{1}H NMR ($CDCl_3$): δ 0.00 (s, 6 H). 0.89 (s, 9 H), 1.21 - 1.33 (m, 0.5 H), 1.43 - 1.52 (m, 0.5 H), 1.55 - 1.68 (m, 0.5 H), 1.75 - 1.88 (m, 0.5 H), 1.91 - 2.31 (m, 3 H), 2.38 -

2.50 (m, 2.5 H), 2.55 - 2.68 (m, 0.5), 2.78 -2.89 (m, 0.5 H), 2.95 (dd, 0.5 H), 3.45 (dd, 1 H), 3.52 - 3.60 (m, 1 H), 7.13 - 7.32 (m, 5 H).

Step K: 4-Methoxybenzyl (1-(R and S)-3-(S)-t-butyldimethylsilyloxymethyl-4-(S)-phenylcyclopent-1-yl)acetate

To a solution of (1-(R and S)-3-(S)-t-butyldimethylsilyloxymethyl-4-(S)-phenylcyclopent-1-yl)acetic acid (4.5 g, 13 mmol) in DMF (120 mL) was added triethylamine (2.3 mL, 1.7 g, 17 mmol) and 4-methoxybenzyl chloride (2.1 mL, 2.4 g, 15 mmol). The reaction mixture was stirred at rt for 12 h. TLC analysis showed only 10% conversion to the desired product. Additional triethylamine (4.6 mL, 3.4 g, 34 mmol) and 4-methoxybenzyl chloride (4.2 mL, 4.8 g, 30 mmol) were added. The reaction mixture was stirred at rt for an additional 48 h until TLC analysis indicated the reaction was complete. The reaction mixture was then diluted with diethyl ether, poured into saturated sodium bicarbonate, extracted three times with diethyl ether. The organic layers were combined, washed with brine, dried over sodium sulfate, filtered, and concentrated. The residue was purified by FC (3% ethyl acetate in hexane) to afford the title product (3.6 g).

^{1}H NMR ($CDCl_3$): δ -0.01 and 0.00 (2 s, 6 H), 0.88 (s, 9 H), 1.23 - 1.33 (m, 1 H), 1.42 - 1.49 (m, 0.5 H), 1.58 - 1.65 (m, 0.5 H), 1.77 - 1.83 (m, 0.5 H), 1.91 - 1.96 (m, 0.5 H), 2.03 (dt, 0.5 H), 2.10 - 2.27 (m, 1.5 H), 2.40 - 2.49 (m, 2.5 H), 2.58 - 2.66 (m, 0.5 H), 2.81 - 2.87 (m, 0.5 H), 2.91 (dd, 0.5 H), 3.44 (dd, 1 H), 3.54 - 3.58 (m, 1 H), 3.83 (s, 3 H), 5.08 (s, 2 H), 6.90 (d, 2 H), 7.17 - 7.28 (m, 3 H), 7.28 - 7.33 (m, 4 H).

Step L: 4-Methoxybenzyl 2-(R and S)-(1-(R and S)-3-(S)-t-butyldimethylsilyloxymethyl-4-(S)-phenylcyclopent-1-yl)-3-(cyclopropyl)propionate

To a solution of 4:1 THF/hexamethylphosphoramide (10 mL) at -78 °C was added 1.5 M lithium diisopropylamide mono(tetrahydrofuran) solution in cyclohexane (0.890 mL, 1.33 mmol). To this solution was then added a solution of 4-methoxybenzyl (1-(R and S)-3-(S)-t-butyldimethylsilyloxymethyl-4-(S)-phenylcyclopent-1-yl)acetate from Step K (0.478 g, 1.02 mmol) in THF (2 mL) and the reaction mixture was stirred at -78 °C for 1 h. To this solution was then added (bromomethyl)cyclopropane (0.495 mL, 0.688 g, 5.10 mmol). The reaction mixture was stirred for 5 h as it was allowed to warm to rt and then diluted with diethyl ether, poured into saturated sodium bicarbonate and extracted three times with diethyl ether.

The organic layers were combined, washed with brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by FC (3% ethyl acetate in hexanes) to afford the title product (0.348 g) as an oil.
^{1}H NMR ($CDCl_3$): δ -0.02, -0.01, 0.00, 0.00, 0.00, and 0.01 (6 s, 6 H), 01 - 0.07 (m, 2 H), 0.36 - 0.43 (m, 2 H), 0.61 - 0.66 (m, 1 H), 0.87, 0.88, 0.88 and 0.89 (4 s, 9 H), 1.18 - 1.24 (m, 0.5 H), 1.30 - 1.39 (m, 0.5 H), 1.41 - 1.52 (m, 1.5 H), 1.54 - 1.62 (m, 1.5 H), 1.68 - 1.72 (m, 0.5 H), 1.78 - 2.02 (m, 1.5 H), 1.85 (t, 0.5 H), 2.09 - 2.28 (m, 1.5 H), 2.38 - 2.46 (m, 1 H), 2.73 - 2.82 (m, 0.5 H), 2.84 - 2.88 (m, 0.5 H), 3.39 - 3.44 (m, 1 H), 3.50 - 3.58 (m, 1 H), 3.81 and 3.84 (2 s, 3 H), 5.02 - 5.15 (m, 2 H), 6.87 (d, 1 H), 6.91 (d, 1 H), 7.16 - 7.20 (m, 3 H), 7.27 - 7.36 (m, 4 H).

Step M: 4-Methoxybenzyl 2-(R or S)-(1-(R and S)-3-(S)-hydroxymethyl-4-(S)-phenylcyclopent-1-yl)-3-(cyclopropyl)propionate and 4-methoxybenzyl 2-(S or R)-(1-(R and S)-3-(S)-hydroxymethyl-4-(S)-phenylcyclopent-1-yl)-3-(cyclopropyl)propionate

To a solution of 4-methoxybenzyl 2-(R and S)-(1-(R and S)-3-(S)-t-butyldimethylsilyloxymethyl-4-(S)-phenylcyclopent-1-yl)-3-(cyclopropyl)propionate from Step L (0.067 g, 0.128 mmol) in THF (2 mL) was added a 1.0 M solution of tetrabutylammonium fluoride in THF (0.192 mL, 0.192 mmol) and the reaction mixture was stirred at rt for 1.25 h. TLC analysis showed that the reaction was not complete and 1.0 M solution of tetrabutylammonium fluoride in THF (0.080 mL, 0.080 mmol) was added. After 2 h, the reaction mixture was diluted with ethyl acetate, poured into 5% aqueous hydrochloric acid solution, extracted three times with ethyl acetate, combined organic layers, washed with brine, dried over sodium sulfate and concentrated to afford 0.071 g. The residue was purified by FC (1-3% ethyl acetate in methylene chloride) to afford separation at the 2-position of the 3-(cyclopropyl)propionate to give the higher R_f isomer (0.023 g) and lower R_f isomer (0.022 g) title compounds as a mixture of the two possible cyclopentyl C-1 diastereomers, but stereochemistries were not assigned.
(higher R_f): ^{1}H NMR ($CDCl_3$): δ -0.01 - 0.08 (m, 2 H), 0.36 - 0.44 (m, 2 H), 0.62 - 0.67 (m, 1 H), 0.83 - 0.92 (m, 0.5 H), 1.12 - 1.19 (m, 0.5 H), 1.38 - 1.42 (br s, 0.5 H), 1.44 - 1.50 (m, 0.5 H), 1.53 - 1.61 (m, 1.5 H), 1.63 -1.71 (m, 0.5 H), 1.81 - 1.93 (m, 1.5 H), 2.00 - 2.05 (m, 0.5 H), 2.14 - 2.27 (m, 2 H), 2.40 - 2.48 (m, 1 H), 2.66 - 2.72 (m, 0.5 H), 2.78 (dd, 0.5 H), 3.44 - 3.49 (m, 1 H), 3.58 - 3.66 (m, 1 H), 3.79 and 3.80

(2 s, 3 H), 5.03 - 5.12 (m, 2 H), 6.87 (d, 2 H), 7.17 - 7.22 (m, 3 H), 7.28 - 7.31 (m, 4 H).

(lower R_f): ^{1}H NMR ($CDCl_3$): δ –0.04 - 0.09 (m, 2 H), 0.35 - 0.43 (m, 2 H), 0.59 - 0.67 (m, 1 H), 0.85 - 0.92 (m, 0.5 H), 1.18 - 1.36 (m, 2 H), 1.39 - 1.46 (m, 1 H), 1.54 - 1.59 (m, 1 H), 1.62 - 1.78 (m, 0.5 H), 1.82 - 1.89 (m, 0.5 H), 1.92 - 2.07 (m, 1 H), 2.13 - 2.22 (m, 1 H), 2.24 - 2.31 (m, 0.5 H), 2.37 - 2.49 (m, 1 H), 2.69 - 2.75 (m, 0.5 H), 2.76 - 2.82 (m, 0.5 H), 3.43 - 3.49 (m, 1 H), 3.56 - 3.61 (m, 1 H), 3.83 (s, 3 H), 5.12 (s, 2 H), 6.91 (d, 2 H), 7.18 - 7.22 (m, 3 H), 7.27 - 7.36 (m, 4 H).

Step N: 4-Methoxybenzyl 2-(S or R)-(1-(R and S)-3-(S)-formyl-4-(S)-phenylcyclopent-1-yl)-3-(cyclopropyl)propionate

To a solution of oxalyl chloride (0.130 mL, 0.189 g, 1.49 mmol) in methylene chloride (4 mL) at -70 °C was added dropwise DMSO (0.212 mL, 0.233 g, 2.98 mmol). After 10 min, a solution of 4-methoxybenzyl 2-(S or R)-(1-(R and S)-3-(S)-hydroxymethyl-4-(S)-phenylcyclopent-1-yl)-3-(cyclopropyl)propionate the lower R_f isomer from Step M (0.122 g, 0.299 mmol) in methylene chloride (1 mL) was added dropwise. The reaction mixture was stirred at -70 °C for 40 min and then triethylamine (0.624 mL, 0.453 g, 4.48 mmol) was added. The reaction mixture was allowed to warm to rt for 10 min and then diluted with methylene chloride, poured into water, and extracted three times with methylene chloride. The organic layers were combined, washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude title compound was used directly in Step O.

Step O: 4-Methoxybenzyl 2-(S or R)-(1-(R)-3-(S)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-3-(cyclopropyl)propionate (faster, minor) and 4-methoxybenzyl 2-(S or R)-(1-(S)-3-(S)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-3-(cyclopropyl)propionate (slower, major)

To a solution of 4-methoxybenzyl 2-(S or R)-(1-(R and S)-3-(S)-formyl-4-(S)-phenylcyclopent-1-yl)-3-(cyclopropyl)propionate from Step N (0.063 g, 0.155 mmol) in 1,2-dichloroethane (2 mL) was added 4-(3-(4-fluorophenyl)prop-1-yl)piperidine hydrochloride (0.041 g, 0.170 mmol) and DIPEA (0.030 mL, 0.022 g, 0.170 mmol). After 10 min, sodium triacetoxyborohydride (0.066 g, 0.310 mmol)

was added. The reaction mixture was stirred at rt for 30 min, diluted with methylene chloride, poured into aqueous sodium bicarbonate and extracted three times with methylene chloride. The organic layers were combined, washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to afford 0.094 g. The residue was purified by prep TLC eluting with 2% MeOH in methylene chloride. The C-1 cyclopentyl diastereomers were then separated using a Chiracel AD column (5% isopropyl alcohol in hexanes) to afford the title compounds, the faster, minor isomer (0.013 g) and the slower, major isomer (0.037 g).

Step P: 2-(S or R)-(1-(R)-3-(S)-((4-(3-(4-Fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-3-(cyclopropyl)propionic acid (minor) and 2-(S or R)-(1-(S)-3-(S)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-3-(cyclopropyl)propionic acid (major)

The individual products from Step O were each taken up in 96% formic acid (1 mL) and stirred at rt for 18.5 h. The formic acid was removed under a stream of nitrogen and each residue was dissolved in methylene chloride, poured into saturated sodium bicarbonate, and extracted three times with methylene chloride. The organic layers were combined for each, washed with brine, dried over sodium sulfate, filtered and concentrated. The residues were purified by prep TLC eluting with 84:14:1:1 methylene chloride/methanol/ammonium hydroxide/water to afford to the two cyclopentyl C-1 title compounds, the minor isomer (0.0043 g) and the major isomer (0.014 g). The stereochemistry at the 2-position of the 3-(cyclopropyl)propionic acid was not assigned.

Step Q 2-(S or R)-(1-(R)-3-(S)-((4-(3-(4-Fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-3-(cyclopropyl)propionic acid hydrochloride salt (minor) and 2-(S or R)-(1-(S)-3-(S)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-3-(cyclopropyl)propionic acid hydrochloride salt (major)

The individual products from Step P were each taken up in 1:1 methylene chloride:diethyl ether (0.5 mL) and 1 N hydrochloric acid in diethyl ether was added (0.026 mL, 26 mmol) to the minor isomer and (0.082 mL, 82 mmol) to the major isomer. The volatiles were removed under a stream of nitrogen to afford the title compounds as white solids.

HPLC/MS (ESI): m/z 491 (M + 1) (for each isomer).

EXAMPLE 12

2-(R or S)-(1-(R or S)-3-(S)-((4-(3-(4-Fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-3-(cyclobutyl)propionic acid hydrochloride salt (higher, minor) and 2-(R or S)-(1-(S or R)-3-(S)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-3-(cyclobutyl)propionic acid hydrochloride salt (lower, major)

Using essentially the same procedure as in Example 11, Steps L-Q, but substituting (bromomethyl)cyclobutane in Step L, the higher isomer from Step M was elaborated to afford the title compounds. Separation of the C-1 cyclopentyl diastereomers was achieved after Step P by prep TLC eluting with 84:14:1:1 methylene chloride:methanol:ammonium hydroxide:water to produce the higher isomer (0.0015 g) and the lower isomer (0.0082 g). Stereochemistries were not assigned.

HPLC/MS (ESI): m/z 506 (M + 1) (for each isomer).

EXAMPLE 13

2-(S or R)-(1-(R)-3-(S)-((4-(3-(4-Fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-3-(cyclobutyl)propionic acid hydrochloride salt (minor) and 2-(S or R)-(1-(S)-3-(S)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-)-4-(S)-phenylcyclopent-1-yl)-3-(cyclobutyl)propionic acid hydrochloride salt (major)

Using essentially the same procedure as in Example 11, Steps L-Q, substituting (bromomethyl)cyclobutane in Step L, the lower R_f isomer from Step M was elaborated to afford the title compounds, the minor isomer (0.0021 g) and the major isomer (0.0013 g). The C-1 cyclopentyl diastereomers were separated using a Chiracel AD column (5% isopropyl alcohol in hexanes) after Step O. The stereochemistry at the 2-position of the 3-(cyclobutyl)propionic acid was not assigned.

HPLC/MS (ESI): m/z 506 (M + 1) (for each isomer).

EXAMPLE 14

2-(S or R)-(1-(R)-3-(S)-((4-(3-(4-Fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)cyclohexylacetic acid hydrochloride salt (minor) and 2-(S or

R)-(1-(S)-3-(S)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)cyclohexylacetic acid hydrochloride salt (major)

Step A 4-Methoxybenzyl 2-(R and S)-(1-(R and S)-3-(S)-t-butyldimethylsilyloxymethyl-4-(S)-phenylcyclopent-1-yl)cyclohex-2-en-1-ylacetate

Using essentially the same procedure as in Example 11, Steps A-L, but substituting 3-bromocyclohexene in Step L, the title compound was prepared (0.080 g).

^{1}H NMR ($CDCl_3$): δ -0.07, -0.06, -0.05, -0.04 and -0.03 (5 s, 6 H), 0.82 and 0.84 (2 s, 9 H), 1.14 - 1.27 (m, 0.5 H), 1.28 -1.42 (m, 1 H), 1.43 - 1.55 (m, 1 H), 1.66 - 1.83 (m, 3 H), 1.83 - 1.88 (m, 1 H), 1.90 - 2.03 (m, 3 H), 2.05 - 2.18 (m, 2 H), 2.28 - 2.38 (m, 0.5 H), 2.39 - 2.54 (m, 1.5 H), 2.55 - 2.70 (m, 0.5 H), 2.72 - 2.85 (m, 1 H), 3.33 - 3.42 (m, 1 H), 3.46 - 3.58 (m, 1 H), 3.77 and 3.79 (2 s, 3 H), 4.95 - 5.13 (m, 2 H), 5.58 - 5.72 (m, 2 H), 6.82 - 6.90 (m, 2 H), 7.10 - 7.18 (m, 3 H), 7.22 - 7.33 (m, 4 H).

Step B 4-Methoxybenzyl 2-(R and S)-(1-(R and S)-3-(S)-t-butyldimethylsilyloxymethyl-4-(S)-phenylcyclopent-1-yl)cyclohexyl-1-ylacetate

A solution of 4-methoxybenzyl 2-(R and S)-(1-(R and S)-3-(S)-t-butyldimethylsilyloxymethyl-4-(S)-phenylcyclopent-1-yl)cyclohex-2-en-1-ylacetate from Step A (0.080 g, 0.146 mmol) in methanol (2 mL) was hydrogenated with palladium on carbon (0.020 g) at 45 psi for 45 min. The catalyst was filtered off and the volatiles removed *in vacuo* to give 0.080 g of a residue which was taken on to Step C without purification.

Step C 2-(S or R)-(1-(R)-3-(S)-((4-(3-(4-Fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)cyclohexylacetic acid hydrochloride salt (minor) and 2-(S or R)-(1-(S)-3-(S)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)cyclohexylacetic acid hydrochloride salt (major)

Using essentially the same procedure as in Example 11, Steps M-Q, 4-methoxybenzyl 2-(R and S)-(1-(R and S)-3-(S)-t-butyldimethylsilyloxymethyl-4-(S)-phenylcyclopent-1-yl)cyclohexyl-1-ylacetate (0.080 g, 0.15 mmol) from Step B was elaborated to afford the title compounds, the minor isomer (0.0011 g) and the major

isomer (0.0033 g). The cyclopentyl C-1 diastereomers were separated using a Chiracel AD column (5% isopropyl alcohol in hexanes) after Step O. The stereochemistry at the 2-position of the lower cyclohexylacetate in Step M was not assigned.
HPLC/MS (ESI): m/z 519 (M + 1) (for each isomer).

5

EXAMPLE 15

2-(R or S)-(1-(R)-3-(S)-((4-(3-(Phenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-3-(cyclobutyl)propionic acid hydrochloride salt (higher) and 2-(R or S)-(1-(S)-3-(S)-((4-(3-(phenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-
10 phenylcyclopent-1-yl)-3-(cyclobutyl)propionic acid hydrochloride salt (lower)

Using essentially the same procedure as in Example 11, Steps M-Q, but substituting 4-(3-(phenyl)prop-1-yl)piperidine hydrochloride in Step O, the higher R_f isomer from Step M was elaborated to afford the title compounds, the higher
15 isomer (0.0098 g) and the lower isomer (0.0017 g). Separation of the cyclopentyl C-1 diastereomers was achieved after Step O by prep TLC eluting with 2% MeOH in methylene chloride. Stereochemistry at the 2-position of the 3-(cyclobutyl)propionic acid was not assigned.
HPLC/MS (ESI): m/z 488 (M + 1) (for each isomer).

20

EXAMPLE 16

2-(S or R)-(1-(R and S)-3-(S)-((4-(3-(Phenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-3-(cyclobutyl)propionic acid hydrochloride salt

25 Using essentially the same procedure as in Example 11, Steps M-Q, but substituting 4-(3-(phenyl)prop-1-yl)piperidine hydrochloride in Step O, the lower R_f isomer from Step M was elaborated to afford the title compound (0.0098 g). No separation of the cyclopentyl C-1 diastereomers was achieved.
HPLC/MS (ESI): m/z 488 (M + 1).

30

EXAMPLE 17

2-(S or R)-(1-(R)-3-(S)-((4-(3-Benzyl-1-ethyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-3-(cyclopropyl)propionic acid hydrochloride salt (minor) and 2-(S or R)-(1-(S)-3-(S)-((4-(3-benzyl-1-ethyl-(1H)-pyrazol-5-

yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-3-(cyclopropyl)propionic acid hydrochloride salt (major)

Using essentially the same procedure as in Example 11, Steps M-Q, substituting 4-(3-benzyl-1-ethyl-(1H)-pyrazol-5-yl)piperidine hydrochloride in Step O, the lower R_f isomer from Step M was elaborated to afford the title compounds, the minor isomer (0.0011 g) and the major isomer (0.0054 g). The cyclopentyl C-1 diastereomers were separated using a Chiracel AD column (5% isopropyl alcohol in hexanes) after Step O. The stereochemistry at the 2-position of the propionic acid was not assigned.

HPLC/MS (ESI): m/z 540 (M + 1) (for each isomer).

EXAMPLE 18

2-(S or R)-(1-(R)-3-(S)-((4-(3-(Quinolin-3-yl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-3-(cyclopropyl)propionic acid di-hydrochloride salt (minor) and 2-(S or R)-(1-(S)-3-(S)-((4-(3-(quinolin-3-yl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-3-(cyclopropyl)propionic acid di-hydrochloride salt (major)

Using essentially the same procedure as in Example 11, Steps M-Q, but substituting 4-(3-(quinolin-3-yl)prop-1-yl)piperidine di-hydrochloride in Step O, the lower R_f isomer from Step M was elaborated to afford the title compounds, the minor isomer (0.0006 g) and the major isomer (0.0048g). The cyclopentyl C-1 diastereomers were separated using a Chiracel AD column (25% isopropyl alcohol in hexanes) after Step O. The stereochemistry at the 2-position of the propionic acid was not assigned.

HPLC/MS (ESI): m/z 525 (M + 1) (for each isomer).

EXAMPLE 19

2-(S or R)-(1-(R)-3-(S)-((4-(*N*-(Propyl)-*N*-(pyrrimidin-2-yl)aminopiperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-3-(cyclopropyl)propionic acid di-hydrochloride salt (minor) and 2-(S or R)-(1-(S)-3-(S)-((4-(*N*-(propyl)-*N*-(pyrrimidin-2-yl)aminopiperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-3-(cyclopropyl)propionic acid di-hydrochloride salt (major)

Using essentially the same procedure as in Example 11, Steps M-Q, substituting 4-(*N*-(propyl)-*N*-(pyrrimidin-2-yl)amino)piperidine di-hydrochloride in Step O, the lower R_f isomer from Step M was elaborated to afford the title compounds, the minor isomer (0.0038 g) and the major isomer (0.016 g). The cyclopentyl C-1 diastereomers were separated using a Chiracel AD column (1% ethanol in hexanes) after Step O. The stereochemistry at the 2-position of the propionic acid was not assigned.
HPLC/MS (ESI): m/z 491 (M + 1) (for each isomer).

EXAMPLE 20

(1-(R or S)-Hydroxy-3-(S)-((4-(3-(4-phenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)acetic acid hydrochloride salt and (1-(S or R)-hydroxy-3-(S)-((4-(3-(4-phenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)acetic acid hydrochloride salt

Step A: (+)-*trans*-3-Formyl-4-phenylcyclopentan-1-one

To a solution of oxalyl chloride (0.352 mL, 0.512 g, 4.03 mmol) in methylene chloride (8 mL) at -70 °C was added dropwise DMSO (0.573 mL, 0.630 g, 8.06 mmol). After 10 min, a solution of (+)-*trans*-3-hydroxymethyl-4-phenylcyclopentan-1-one from Example 11, Step F (0.153 g, 0.807 mmol) in methylene chloride (1 mL) was added dropwise. The reaction mixture was stirred at -70 °C for 45 min and then diisopropylethylamine (2.1 mL, 1.6 g, 4.48 mmol) was added. The reaction mixture was allowed to warm to rt for 10 min and then diluted with methylene chloride, poured into water, and extracted three times with methylene chloride. The organic layers were combined, washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude title compound (0.15 g) was used directly in Step B.

Step B: (+)-*trans*-4-((3-(Phenyl)prop-1-yl)piperidin-1-yl)methyl-4-phenylcyclopentan-1-one

To a solution of (+)-*trans*-3-formyl-4-phenylcyclopentan-1-one from Step A (0.15 g, 0.807 mmol) in 1,2-dichloroethane (8 mL) was added 4-(3-(phenyl)prop-1-yl)piperidine hydrochloride (0.212 g, 0.888 mmol) and DIPEA (0.155 mL, 0.115 g, 0.888 mmol). After 10 min, sodium triacetoxyborohydride (0.342 g, 1.6 mmol) was added. The reaction mixture was stirred at rt for 10 min, diluted with methylene chloride, poured into aqueous sodium bicarbonate and extracted three

times with methylene chloride. The organic layers were combined, washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by FC (50% ethyl acetate in hexanes) to afford the title compound (0.136 g).
HPLC/MS (ESI): m/z 375 (M + 1)

Step C: Ethyl (1-(R or S)-hydroxy-3-(S)-((4-(3-(4-phenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)acetate and ethyl (1-(S or R)-hydroxy-3-(S)-((4-(3-(4-phenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)acetate

A solution of (+)-*trans*-4-((3-(phenyl)prop-1-yl)piperidin-1-yl)methyl-4-phenylcyclopentan-1-one from Step B (0.044 g, 0.117 mmol) and α-bromoacetate (0.017 mL, 0.025 g, 0.152 mmol) in THF (0.2 mL) was added to a 0.1 M solution in THF of samarium iodide (2.3 mL, 0.234 mmol). The reaction mixture was stirred at rt for 5 min, poured into water, and extracted three times with ethyl acetate. The organic layers were combined, washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford the title compound (0.043 g) which was used in the next step without further purification.
HPLC/MS (ESI): m/z 463 (M + 1)

Step D: (1-(R or S)-Hydroxy-3-(S)-((4-(3-(4-phenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)acetic acid and (1-(S or R)-hydroxy-3-(S)-((4-(3-(4-phenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)acetic acid

To a solution of ethyl (1-(R or S)-hydroxy-3-(S)-((4-(3-(4-phenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)acetate and ethyl (1-(S or R)-hydroxy-3-(S)-((4-(3-(4-phenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)acetate from Step C (0.043 g, 0.093 mmol) in ethanol (1 mL) was added 5N sodium hydroxide solution (0.028 mL, 0.139 mmol). The reaction mixture was stirred at rt for 5 h and then acidified with 2N hydrochloric acid until the pH = 7 and concentrated *in vacuo*. The residue was purified by prep TLC eluting with 84:14:1:1 methylene chloride/methanol/ammonium hydroxide/water and separation of the C-1 diastereomers was achieved to afford the title compounds, the higher R_f isomer (0.0058 g) and the lower R_f isomer (0.0048 g). Stereochemistries were not assigned.
HPLC/MS (ESI): m/z 436 (M + 1) (for each isomer)

Step E (1-(R or S)-Hydroxy-3-(S)-((4-(3-(4-phenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)acetic acid hydrochloride salt and (1-(S or R)-hydroxy-3-(S)-((4-(3-(4-phenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)acetic acid hydrochloride salt

The individual isomers from Step D were each taken up in 1:1 methylene chloride:diethyl ether (0.5 mL) and 1 N hydrochloric acid in diethyl ether was added (0.040 mL, 40 mmol) to the higher isomer and (0.033 mL, 33 mmol) to the lower isomer. The volatiles were removed under a stream of nitrogen to afford the title compounds as white solids.

HPLC/MS (ESI): m/z 436 (M + 1) (for each isomer).

EXAMPLE 21

2-(S or R)-(1-(R)-3-(S)-((4-(3-Benzyl-1-ethyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionic acid di-hydrochloride salt

Step A: Methyl (+-)-*trans*-4-methylene-2-(3-fluorophenyl)cyclopentanoate

A mixture of methyl *trans*-3-fluorocinnamate (41.25 g, 229 mmol), tetrakis(triphenylphosphine) palladium(0) (18.5 g, 16 mmol), 1,2-bis(diphenylphosphino)ethane (5.5 g, 13.7 mmol) and 2-((trimethylsilyl)methyl)-2-propen-1-yl acetate (42.66 g, 229 mmol) in THF (300 mL) under nitrogen was heated to reflux for 6 h and then stirred at rt for 16 h. The reaction was diluted with hexane and filtered to remove yellow precipitate. The volatiles were then removed *in vacuo* and the residue was purified by FC (3 to 5% ethyl acetate in hexanes) to afford the title compound (45 g).

^{1}H NMR ($CDCl_3$) δ: 2.52 (m, 1 H), 2.68 (m, 1 H), 2.8-2.9 (m, 2 H), 2.95 (ddd, 1 H), 3.45 (ddd, 1 H), 3.63 (s, 3 H), 4.96 (m, 2 H), 6.9-7.0 (m, 2 H), 7.03 (d, 1 H), 7.2-7.3 (m, 1 H).

Step B: (+-)-*trans*-4-Methylene-2-(3-fluorophenyl)cyclopentanoic acid

To a solution of methyl (+-)-*trans*-4-methylene-2-(3-fluoro)phenylcyclopentanoate prepared as in Step A (47 g, 200 mmol) in methanol (500 mL) was added 5N sodium hydroxide (200 mL, 1000 mmol). The reaction was

stirred at rt for 60 h then concentrated *in vacuo*. The residue was taken up in water, acidified with 2M hydrochloric acid and extracted twice with methylene chloride. The organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated *in vacuo* to give the crude title acid (40.8 g) which was used directly in Step C.

Step C: (+)-*trans*-1-Hydroxymethyl-4-methylene-2-(3-fluorophenyl)cyclopentane and (-)-*trans*-1-hydroxymethyl-4-methylene-2-(3-fluorophenyl)cyclopentane

A solution of (+-)-*trans*-4-methylene-2-(3-fluorophenyl)cyclopentanoate (5.2 g, 23.6 mmol) from Step B in THF (100 mL) was cooled to 0 °C under nitrogen and 1M lithium aluminum hydride (LAH) in THF (35.4 mL) was added dropwise over 10 min. The reaction was stirred at rt for 16 h, the excess LAH was quenched by dropwise addition of acetone and the reaction was then poured into dilute aq. HCl. The mixture was extracted twice with ether and the organic layers were washed with brine, dried over sodium sulfate, combined and concentrated. The residue was purified by FC (25% ethyl acetate in hexanes) to afford the racemic title product (4.1 g) as a an oil. Chiral Prep HPLC on a 2 cm x 25 cm Chiracel OD column eluting with 5% isopropanol in hexanes (25 injections) afforded the (-)-enantiomer, $[\alpha]_D$ = -45.5 (MeOH, c = 0.9), as the first eluting peak (R_t = 17.5 min) and the (+)-enantiomer (1.87 g), $[\alpha]_D$ = +45.0 (MeOH, c = 1.0), as the second peak (R_t = 22.0 min).

^{1}H NMR ($CDCl_3$) δ: 2.2-2.35 (m, 2 H), 2.5 (m, 1 H), 2.65-2.85 (m, 2 H), 2.9 (m, 1 H), 3.51 and 3.68 (dABq, 2 H), 4.93 (m, 2 H), 6.9-7.0 (m, 2 H), 7.06 (d, 1 H), 7.3-7.4 (m, 1 H).

Step D: (+)-*trans*-3-Hydroxymethyl-4-(3-fluorophenyl)cyclopentan-1-one

A solution of (+)-*trans*-1-hydroxymethyl-4-methylene-2-(3-fluorophenyl)cyclopentane from Step C (1.87 g, 9.0 mmol) in methanol (75 mL) was cooled in a dry ice/acetone bath and ozone was bubbled into the solution until the blue color persisted. The excess ozone was removed with a stream of nitrogen and then dimethylsulfide (5 mL) was added. After 10 min, the bath was removed and the reaction was allowed to warm to rt over 2 h. The mixture was treated with 10 drops of sulfuric acid (c) in water (2 mL) for 1 h before most of the methanol was removed *in vacuo*. The mixture was diluted with water and extracted twice with ethyl acetate

and the organic layers were washed with brine, dried over sodium sulfate, combined and concentrated. The residue was purified by FC (50% ethyl acetate in hexanes) to give the title compound (1.87 g)), $[\alpha]_D$ = +132 (MeOH, c = 1.2),.
^{1}H NMR ($CDCl_3$) δ: 2.3-2.45 (m, 2 H), 2.5 (m, 1 H), 2.61 and 2.77 (dABq, 2 H), 2.28 (ddd, 1 H), 3.61 and 3.75 (dABq, 2 H), 6.9-7.0 (m, 2 H), 7.06 (d, 1 H), 7.3-7.4 (m, 1 H).

Step E: (+)-*trans*-1-t-Butyldimethylsilyloxymethyl-4-oxo-2-(3-fluorophenyl)cyclopentane

To a solution of (+)-*trans*-3-hydroxymethyl-4-(3-fluorophenyl)cyclopentan-1-one from Step D (6.23 g, 29.9 mmol) in methylene chloride (100 mL) was added DIPEA (16.0 mL, 11.6 g, 89.7 mmol) and t-butyldimethylsilyl chloride (6.80 g, 44.8 mmol). The reaction mixture was stirred at rt for 48 h, poured into aqueous sodium bicarbonate, and extracted three times with methylene chloride. The organic layers were combined, washed with brine, dried over sodium sulfate, filtered and concentrated. The residue (12 g) was purified by FC (5% ethyl acetate in hexanes) to afford the title product (8.99 g) as a oil.
^{1}H NMR ($CDCl_3$) δ 0.02 (s 3 H), 0.03 (s, 3 H), 0.90 (s, 9 H), 2.36 - 2.55 (m, 4 H), 2.73 (dd, 1 H), 3.31 - 3.38 (m, 1 H), 3.54 (dd, 1 H), 3.62 (dd, 1 H), 6.93 - 7.05 (m, 3 H), 7.27 - 7.34 (m, 1 H).

Step F: Ethyl (E and Z)-3-(S)-t-butyldimethylsilyloxymethyl-4-(S)-(3-fluorophenyl)cyclopent-1-ylideneacetate

To a solution of 60% sodium hydride in mineral oil (3.0 g, 76 mmol) in THF (100 mL) was added triethyl phosphonoacetate (19 mL, 21 g, 95 mmol). The reaction mixture was stirred at rt for 30 min. To this solution was added via canula a solution of (+)-*trans*-1-t-butyldimethylsilyloxymethyl-4-oxo-2-(3-fluorophenyl)cyclopentane from Step E (6.13 g, 19 mmol) in THF (20 mL). The reaction mixture was stirred at rt for 12 h, diluted with diethyl ether, poured into water and extracted three times with diethyl ether. The organic layers were combined, washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude residue (7.45 g) was taken on to Step G without further purification.

Step G: Ethyl (E and Z)-3-(S)-hydroxymethyl-4-(S)-(3-fluorophenyl)cyclopent-1-ylideneacetate

To a solution of ethyl (E and Z)-3-(S)-t-butyldimethylsilyloxymethyl-4-(S)-(3-fluorophenyl)cyclopent-1-ylideneacetate from Step F (7.45 g, 19 mmol) in THF (100 mL) was added a 1.0 M solution of tetrabutylammonium fluoride in THF (39 mL, 39 mmol) and the reaction mixture was stirred at rt for 4 h. The reaction mixture was diluted with ethyl acetate, poured into 1 N aqueous hydrochloric acid solution, extracted three times with ethyl acetate, combined organic layers, washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by FC (5% ethyl acetate in hexanes) to afford the title compound (3.03 g).
^{1}H NMR ($CDCl_3$): δ 1.25 and 1.28 (2 t, 3 H), 2.05 - 2.39 (m, 1 H), 2.49 - 2.57 (m, 0.5 H), 2.65 - 2.74 (m, 1 H), 2.79 - 2.92 (m, 1 H), 2.95 - 3.01 (m, 1 H), 3.22 (d, 0.5 H), 3.33 (dd, 0.5 H), 3.47 - 3.59 (m, 1.5 H), 3.63 - 3.74 (m, 1 H), 4.13 and 4.17 (2 q, 2 H), 5.83 (br s, 1 H), 6.90 - 7.00 (m, 2 H), 7.15 (d, 1 H), 7.23 - 7.35 (m, 1 H).

Step H: Ethyl (1-(R)-3-(S)-hydroxymethyl-4-(S)-(3-fluorophenyl)cyclopent-1-yl)acetate

A solution of ethyl (E and Z)-3-(S)-hydroxymethyl-4-(S)-(3-fluorophenyl)cyclopent-1-ylideneacetate from Step G (3.62 g, 13 mmol) in methylene chloride (150 mL) was hydrogenated at atmospheric pressure using (1,5-cyclooctadiene)(pyridine)(tricyclohexylphosphine)iridium(I) hexafluorophosphate (0.250 g) for 12 h. The volatiles were removed *in vacuo* to afford the title compound (3.64 g) as essentially a single cyclopentyl C-1 isomer which then was used crude in Step I. Note that the stereochemistry at the cyclopentyl C-1 in this example, using the 3-hydroxymethyl intermediate and the above catalyst, affords essentially only the 1,3-trans product whereas the 1,3-trans compound was only the minor product from reduction of the 3-t-butyldimethylsilyloxymethyl intermediate with 10% Pd/C as in Example 1, Step F and Example 11, Step I.
^{1}H NMR ($CDCl_3$): δ 1.27 (t, 3 H), 1.41 - 1.54 (m, 1 H), 1.65 - 1.73 (m, 1 H), 1.88 - 1.95 (m, 1 H), 2.22 - 2.32 (m, 2 H), 2.41 - 2.50 (m, 3 H), 2.78 - 2.85 (m, 1 H), 3.51 (dd, 1 H), 3.63 (dd, 1 H), 4.14 (m, 2 H), 6.87 - 6.97 (m, 2 H), 7.02 (d, 1 H), 7.23 - 7.29 (m, 1 H).

Step I: Ethyl (1-(R)-3-(S)-t-butyldimethylsilyloxymethyl-4-(S)-(3-fluorophenyl)cyclopent-1-yl)acetate

To a solution of ethyl (1-(R)-3-(S)-hydroxymethyl-4-(S)-(3-fluorophenyl)cyclopent-1-yl)acetate from Step H (3.64 g, 13.0 mmol) in methylene

chloride (130 mL) was added DIPEA (6.8 mL, 5.0 g, 39 mmol) and t-butyldimethylsilyl chloride (2.94 g, 19.5 mmol). The reaction mixture was stirred at rt for 3 days, poured into aqueous sodium bicarbonate, and extracted three times with methylene chloride. The organic layers were combined, washed with brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by FC (3% ethyl acetate in hexanes) to afford the title compound (4.55 g).

Step J: (1-(R)-3-(S)-t-Butyldimethylsilyloxymethyl-4-(S)-(3-fluorophenyl)cyclopent-1-yl)acetic acid

To a solution of ethyl (1-(R)-3-(S)-t-butyldimethylsilyloxymethyl-4-(S)-(3-fluorophenyl)cyclopent-1-yl)acetate from Step I (4.55 g, 11.5 mmol) in MeOH (100 mL) was added 5.0 N sodium hydroxide solution (12 mL, 58 mmol). The reaction mixture was stirred at rt for 12 h, acidified with 18% citric acid until the pH = 4, diluted with methylene chloride, poured into water, and extracted three times with methylene chloride. The organic layers were combined, washed with brine, dried over sodium sulfate, filtered and concentrated to afford the title compound (4.23 g) which was used in Step K without purification.

Step K: 4-Methoxybenzyl (1-(R)-3-(S)-t-butyldimethylsilyloxymethyl-4-(S)-(3-fluorophenyl)cyclopent-1-yl)acetate

To a solution of (1-(R)-3-(S)-t-butyldimethylsilyloxymethyl-4-(S)-(3-fluorophenyl)cyclopent-1-yl)acetic acid from Step J (4.23 g, 11.5 mmol) in DMF (100 mL) was added pulverized potassium carbonate (4.8 g, 35 mmol) and 4-methoxybenzyl chloride (2.3 mL, 2.7 g, 17 mmol). The reaction mixture was stirred at rt for 12 h, diluted with diethyl ether, poured into saturated sodium bicarbonate, and extracted three times with diethyl ether. The organic layers were combined, washed with brine, dried over sodium sulfate, filtered, and concentrated. The residue was purified by FC (5% ethyl acetate in hexane) to afford the title product (0.300 g). Note: a significant amount of 4-methoxybenzyl (1-(R)-3-(S)-hydroxymethyl-4-(S)-(3-fluorophenyl)cyclopent-1-yl)acetate (4.71 g) was recovered from this reaction. ^{1}H NMR ($CDCl_3$): δ -0.01 (s, 3 H), -0.00 (s, 3 H), 0.87 (s, 9 H), 1.37 - 1.47 (m, 1 H), 1.56 - 1.63 (m, 1 H), 1.87 - 1.95 (m, 1 H), 2.13 - 2.27 (m, 2 H), 2.40 - 2.48 (m, 3 H), 2.82 - 2.89 (m, 1 H), 3.44 (dd, 1 H), 3.52 (dd, 1 H), 3.83 (s, 3 H), 5.07 (s, 2 H), 6.85 - 6.94 (m, 4 H), 6.98 (d, 1 H), 7.20 - 7.33 (m, 3 H).

Step L: 4-Methoxybenzyl 2-(R and S)-(1-(R)-3-(S)-t-butyldimethylsilyloxymethyl-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionate

To a solution of 5:1 THF/hexamethylphosphoramide (6 mL) at -78 °C was added 1.5 M lithium diisopropylamide mono(tetrahydrofuran) solution in cyclohexane (0.534 mL, 0.801 mmol). To this solution was then added a solution of 4-methoxybenzyl (1-(R)-3-(S)-t-butyldimethylsilyloxymethyl-4-(S)-(3-fluorophenyl)cyclopent-1-yl)acetate from Step K (0.300 g, 0.616 mmol) in THF (1 mL) and the reaction mixture was stirred at -78 °C for 40 min. To the reaction mixture was then added (bromomethyl)cyclopropane (0.299 mL, 0.416 g, 3.08 mmol). The reaction mixture was stirred for 3 h as it was allowed to warm to rt and then diluted with diethyl ether, poured into saturated sodium bicarbonate and extracted three times with diethyl ether. The organic layers were combined, washed with brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by FC (3% ethyl acetate in hexanes) to afford the title product (0.232 g) as 1:1 mixture of diastereomers.

^{1}H NMR ($CDCl_3$): δ -0.02, -0.01 and -0.00 (3 s, 6 H), 0.02 - 0.05 (m, 2 H), 0.36 - 0.42 (m, 2 H), 0.61 - 0.65 (m, 1 H), 0.86 and 0.86 (2 s, 9 H), 1.21 - 1.50 (m, 3 H), 1.52 - 1.62 (m, 2 H), 1.64 - 1.75 (m, 0.5 H), 1.82 - 1.89 (m, 0.5 H), 1.95 - 2.01 (m, 0.5 H), 2.08 - 2.26 (m, 2.5 H), 2.38 - 2.47 (m, 1 H), 3.38 - 3.44 (m, 1 H), 3.47 - 3.52 (m, 1 H), 3.80 and 3.83 (s, 3 H), 5.04 - 5.32 (m, 2 H), 6.85 - 6.96 (m, 5 H), 7.22 (dd, 1 H), 7.27 - 7.35 (m, 2 H).

Step M: 4-Methoxybenzyl 2-(R or S)-(1-(R)-3-(S)-hydroxymethyl-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionate and 4-methoxybenzyl 2-(S or R)-(1-(R)-3-(S)-hydroxymethyl-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionate

To a solution of 4-methoxybenzyl 2-(R and S)-(1-(R)-3-(S)-t-butyldimethylsilyloxymethyl-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionate from Step L (0.026 g, 0.048 mmol) in THF (1 mL) was added a 1.0M solution of tetrabutylammonium fluoride in THF (0.072 mL, 0.072 mmol) and the reaction mixture was stirred at rt for 12 h. The reaction mixture was diluted with ethyl acetate, poured into 1N aqueous hydrochloric acid solution, extracted three times with ethyl acetate, combined organic layers, washed with brine, dried over sodium sulfate and concentrated to afford 0.018 g. The residue was purified by FC

(5% ethyl acetate in methylene chloride) to afford separation at the 2-position of the 3-(cyclopropyl)propionate to give the higher R_f (0.008 g) and lower R_f (0.009 g) title compounds but the stereochemistries were not assigned.

(higher R_f isomer) ^{1}H NMR ($CDCl_3$): δ -0.01 - 0.01 (m, 2 H), 0.38 - 0.42 (m, 2 H), 0.60 - 0.68 (m, 1 H), 1.42 - 1.50 (m, 2 H), 1.53 - 1.70 (m, 3 H), 1.80 - 1.88 (m, 1 H), 1.99 - 2.06 (m, 1 H), 2.10 - 2.29 (m, 1 H), 2.45 (td, 1 H), 2.68 - 2.75 (m, 1 H), 3.45 (dd, 1 H), 3.59 (dd, 1 H), 3.80 (s, 3 H), 5.07 (s, 2 H), 6.92 - 6.96 (m, 3 H), 6.98 (d, 1 H), 7.10 - 7.16 (m, 4 H).

(lower R_f isomer) ^{1}H NMR ($CDCl_3$): δ -0.02 - 0.02 (m, 2 H), 0.38 - 0.40 (m, 2 H), 0.58 - 0.68 (m, 1 H), 1.38 - 1.44 (m, 2 H), 1.54 - 1.60 (m, 2 H), 1.63 - 1.78 (m, 2 H), 2.13 - 2.33 (m, 2 H), 2.45 (td, 1 H), 2.70 - 2.78 (m, 1 H), 3.46 (dd, 1 H), 3.56 (dd, 1 H), 3.83 (s, 3 H), 5.11 (d, 2 H), 6.93 - 6.96 (m, 3 H), 6.99 (d, 1 H), 7.10 - 7.18 (m, 4 H).

Step N: 4-Methoxybenzyl 2-(S or R)-(1-(R)-3-(S)-formyl-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionate

To a solution of oxalyl chloride (0.008 mL, 0.011 g, 0.089 mmol) in methylene chloride (0.5 mL) at -70 °C was added DMSO (0.013 mL, 0.014 g, 0.180 mmol). After 10 min, a solution of 4-methoxybenzyl 2-(S or R)-(1-(R)-3-(S)-hydroxymethyl-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionate, the lower R_f isomer from Step M, (0.008 g, 0.018 mmol) in methylene chloride (0.5 mL) was added dropwise. The reaction was stirred at -70 °C for 40 min and then triethylamine (0.037 mL, 0.027 g, 0.268 mmol) was added. The reaction mixture was allowed to warm to rt for 10 min and then diluted with methylene chloride, poured into water, and extracted three times with methylene chloride. The organic layers were combined, washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude title compound was used directly in Step O.

Step O: 4-Methoxybenzyl 2-(S or R)-(1-(R)-3-(S)-((4-(3-benzyl-1-ethyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionate

To a solution of 4-methoxybenzyl 2-(S or R)-(1-(R)-3-(S)-formyl-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionate from Step N (0.008 g, 0.018 mmol) in 1,2-dichloroethane (1 mL) was added 4-(3-benzyl-1-ethyl-(1H)-pyrazol-5-yl)piperidine hydrochloride (0.007 g, 0.020 mmol) and DIPEA (0.007 mL,

0.005 g, 0.039 mmol). After 10 min, sodium triacetoxyborohydride (0.007 g, 0.036 mmol) was added. The reaction mixture was stirred at rt for 12 h, diluted with methylene chloride, poured into aqueous sodium bicarbonate and extracted three times with methylene chloride. The organic layers were combined, washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by prep TLC eluting with 5% MeOH in methylene chloride to afford the title compound (0.009 g).

Step P: 2-(S or R)-(1-(R)-3-(S)-((4-(3-Benzyl-1-ethyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionic acid

4-Methoxybenzyl 2-(S or R)-(1-(R)-3-(S)-((4-(3-benzyl-1-ethyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionate from Step O (0.009 g, 0.018 mmol) was taken up in 96% formic acid (1 mL) and stirred at rt for 12 h. The formic acid was removed under a stream of nitrogen. The residue was purified by ion exchange chromatography (0.5 g Varian SCX resin, eluting with 100% MeOH, then with 2.0 M NH_3/MeOH) to afford to the title compound (0.008 g). The stereochemistry at the 2-position of the 3-(cyclopropyl)propionic acid was not assigned.

Step Q 2-(S or R)-(1-(R)-3-(S)-((4-(3-Benzyl-1-ethyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionic acid di-hydrochloride salt

2-(S or R)-(1-(R)-3-(S)-((4-(3-Benzyl-1-ethyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionic acid from Step P (0.008 g, 0.014 mmol) was taken up in 1:1 methylene chloride:ether (0.5 mL) and 1.0 N hydrochloric acid in diethyl ether was added (0.086 mL, 0.086 mmol). The volatiles were removed under a stream of nitrogen to give the title compound as a white solid.

HPLC/MS (ESI): m/z 558 (M + 1).

EXAMPLE 22

2-(R or S)-(1-(R)-3-(S)-((4-(3-Benzyl-1-ethyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionic acid hydrochloride salt

Using essentially the same procedure as in Example 21, Steps L-Q, the higher R_f isomer from Example 21, Step M was elaborated to afford the title compound (0.011 g). The stereochemistry at the 2-position of the propionic acid was not assigned.
HPLC/MS (ESI): m/z 558 (M + 1).

EXAMPLE 23

2-(S or R)-(1-(R)-3-(S)-((4-(3-Benzyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionic acid di-hydrochloride salt

Using essentially the same procedure as in Example 21, Steps O-Q, but substituting 4-(3-benzyl-(1H)-pyrazol-5-yl)piperidine di-hydrochloride in Step O, the title compound (0.020 g) was obtained. The residue in Step O was purified by prep TLC eluting with 10% MeOH in methylene chloride.
HPLC/MS (ESI): m/z 530 (M + 1).

EXAMPLE 24

2-(S or R)-(1-(R)-3-(S)-((4-(4-(2-Phenyleth-1-yl)-1-ethyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionic acid di-hydrochloride salt

Using essentially the same procedure as in Example 21, Steps O-Q, but substituting 4-(4-(2-phenyleth-1-yl)-1-ethyl-(1H)-pyrazol-5-yl)piperidine di-hydrochloride in Step O, the title compound (0.018 g) was obtained.
HPLC/MS (ESI): m/z 572 (M + 1).

EXAMPLE 25

2-(S or R)-(1-(R)-3-(S)-((4-(3-(Quinolin-3-yl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionic acid di-hydrochloride salt

Using essentially the same procedure as in Example 21, Steps O-Q, but substituting 4-(3-(quinolin-3-yl)prop-1-yl)piperidine di-hydrochloride in Step O, the title compound (0.024 g) was obtained. The residue in Step O was purified by prep TLC eluting with 10% MeOH in methylene chloride.

HPLC/MS (ESI): m/z 543 (M + 1).

EXAMPLE 26

2-(S or R)-(1-(R)-3-(S)-((4-(3-(4-Fluorobenzyl)-1-ethyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionic acid di-hydrochloride salt

Using essentially the same procedure as in Example 21, Steps O-Q, but substituting 4-(3-(4-fluorobenzyl)-1-ethyl-(1H)-pyrazol-5-yl)piperidine di-hydrochloride in Step O, the title compound (0.025 g) was obtained.
HPLC/MS (ESI): m/z 576 (M + 1).

EXAMPLE 27

2-(S or R)-(1-(R)-3-(S)-((4-(3-(3,4-Difluorobenzyl)-1-ethyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionic acid di-hydrochloride salt

Using essentially the same procedure as in Example 21, Steps O-Q, but substituting 4-(3-(3,4-difluorobenzyl)-1-ethyl-(1H)-pyrazol-5-yl)piperidine di-hydrochloride in Step O, the title compound (0.020 g) was obtained.
HPLC/MS (ESI): m/z 594 (M + 1).

EXAMPLE 28

2-(S or R)-(1-(R)-3-(S)-((4-(3,3-Difluoro-3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionic acid hydrochloride salt

Using essentially the same procedure as in Example 21, Steps O-Q, but substituting 4-(3,3-difluoro-3-(4-fluorophenyl)prop-1-yl)piperidine hydrochloride in Step O, the title compound was obtained.
HPLC/MS (ESI): m/z 546.3 (M + 1) Rt = 3.97 min.

EXAMPLE 29

2-(S or R)-(1-(R)-3-(S)-((4-(2-(4-Fluorophenylthio)eth-1-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionic acid hydrochloride salt

Using essentially the same procedure as in Example 21, Steps O-Q, but substituting 4-(2-(4-fluorophenylthio)eth-1-yl)piperidine hydrochloride in Step O, the title compound was obtained.

HPLC/MS (ESI): m/z 528.2 (M + 1) Rt = 4.00 min.

EXAMPLE 30

2-(S or R)-(1-(R)-3-(S)-((4-(2-(4-Fluorophenylthio)eth-1-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionic acid, (R) or (S)-sulfoxide hydrochloride salt

Using essentially the same procedure as in Example 21, Steps O-Q, but substituting 4-(2-(4-fluorophenylthio)eth-1-yl)piperidine, (R) or (S)-sulfoxide hydrochloride (faster sulfoxide isomer on reverse phase prep HPLC) in Step O, the title compound was obtained.

HPLC/MS (ESI): m/z 544.0 (M + 1) Rt = 2.79 min.

EXAMPLE 31

2-(S or R)-(1-(R)-3-(S)-((4-(2-(4-Fluorophenylthio)eth-1-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionic acid, (S) or (R)-sulfoxide hydrochloride salt

Using essentially the same procedure as in Example 21, Steps O-Q, but substituting 4-(2-(4-flourophenylthio)eth-1-yl)piperidine, (S) or (R)-sulfoxide hydrochloride (slower sulfoxide isomer on reverse phase prep HPLC) in Step O, the title compound was obtained.

HPLC/MS (ESI): m/z 544.3 (M + 1) Rt = 3.41 min.

EXAMPLE 32

2-(S or R)-(1-(R)-3-(S)-((4-(2-(4-Fluorophenylsulfonyl)eth-1-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionic acid hydrochloride salt

Using essentially the same procedure as in Example 21, Steps O-Q, but substituting 4-(2-(4-fluorophenylsulfonyl)eth-1-yl)piperidine hydrochloride in Step O, the title compound was obtained.
HPLC/MS (ESI): m/z 560.3 (M + 1) Rt = 3.60 min.

EXAMPLE 33

2-(S or R)-(1-(R)-3-(S)-((4-(2-Benzyl-(1H)-imidazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionic acid di-hydrochloride salt

Using essentially the same procedure as in Example 21, Steps O-Q, but substituting 4-(2-benzyl-(1H)-imidazol-5-yl)piperidine di-hydrochloride in Step O, the title compound was obtained.
HPLC/MS (ESI): m/z 530.0 (M + 1) Rt = 2.50 min.

EXAMPLE 34

2-(S or R)-(1-(R)-3-(S)-((4-(3-(4-cyanophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionic acid hydrochloride salt

Using essentially the same procedure as in Example 21, Steps O-Q, but substituting 4-(3-(4-cyanophenyl)prop-1-yl)piperidine hydrochloride in Step O, the title compound was obtained.
HPLC/MS (ESI): m/z 517.3 (M + 1) Rt = 3.89 min.

EXAMPLE 35

2-(S or R)-(1-(R)-3-(S)-((4-(3-(3,4-Difluorobenzyl)-1-methyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionic acid di-hydrochloride salt

Using essentially the same procedure as in Example 21, Steps O-Q, but substituting 4-(3-(3,4-difluorobenzyl)-1-methyl-(1H)-pyrazol-5-yl)piperidine di-hydrochloride in Step O, the title compound (0.020 g) was obtained.
HPLC/MS (ESI): m/z 580.3 (M + 1) Rt = 3.71 min.

EXAMPLE 36

2-(S or R)-(1-(R)-3-(S)-((4-(3-(4-Fluorobenzyl)-1-propyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionic acid di-hydrochloride salt

Using essentially the same procedure as in Example 21, Steps O-Q, but substituting 4-(3-(4-fluorobenzyl)-1-propyl-(1H)-pyrazol-5-yl)piperidine di-hydrochloride in Step O, the title compound was obtained.
HPLC/MS (ESI): m/z 590.3 (M + 1) Rt = 3.81 min.

EXAMPLE 37

2-(S or R)-(1-(R)-3-(S)-((4-(Benzimidazol-1-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionic acid di-hydrochloride salt

Using essentially the same procedure as in Example 21, Steps O-Q, but substituting 4-(benzimadazol-1-yl)piperidine di-hydrochloride in Step O, the title compound was obtained.
HPLC/MS (ESI): m/z 490.3 (M + 1) Rt = 3.01 min.

EXAMPLE 38

2-(E)-(3-(S)-((4-(3-(Benzyl)-1-ethyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-ylidenyl)-3-(cyclopropyl)propionic acid di-hydrochloride salt

Step A: 2-(Diethoxyphosphoryl)acetic acid para-methoxybenzyl ester

To a solution of diethyl phosphonoacetic acid (6.0 g, 30.5 mmol) in 100 ml of DMF was added pulverized potassium carbonate (12.6 g, 91.5 mmol) and 4-methoxybenzyl chloride (6.2 mL, 45.8 mmol). The reaction mixture was stirred 12 h then diluted with diethyl ether, poured into water, and extracted three times with diethyl ether. The organic phases were combined, washed with saturated sodium chloride, dried over sodium sulfate, and filtered. The volatiles were removed *in vacuo* to afford 11 g. The residue was purified by FC (40 – 60% ethyl acetate in hexanes) to afford the title compound (6.04 g).
^{1}H NMR ($CDCl_3$): δ 1.30 (t, 6 H), 2.96 (s, 1 H), 3.02 (s, 1 H), 3.81 (s, 3 H), 4.09 – 4.17 (m, 4 H), 5.12 (s, 2 H), 6.89 (d, 2 H), 7.32 (d, 2 H).

Step B: 2-(Diethoxyphosphoryl)-3-cyclopropylproprionic acid para methoxybenzyl ester

To a suspension of 60% sodium hydride in mineral oil (0.840 g, 21.0 mmol) in DMF (100 mL) was added a solution of 2-(diethoxyphosphoryl)acetic acid para-methoxybenzyl ester (6.04 g, 19.1 mmol) from Step A in DMF (10 mL). The reaction mixture was stirred for 30 min at room temperature. Bromomethylcyclopropane (2.4 mL, 24.8 mmol) was added and the reaction mixture was stirred at rt for 12 h. The reaction mixture was diluted with diethyl ether, poured into saturated sodium bicarbonate, and extracted three times with diethyl ether. The organic layers were combined, washed with saturated sodium chloride, dried over sodium sulfate, and filtered. The volatiles were removed *in vacuo* and the residue was purified by FC (40% ethyl acetate in hexanes) to afford 4.31 g of the title compound. ^{1}H NMR ($CDCl_3$): δ 0.04 – 0.13 (m, 2 H), 0.37 – 0.45 (m, 2 H), 0.68 – 0.73 (m, 1 H), 1.25 – 1.29 (m, 6 H), 1.65 – 1.72 (m, 1 H), 1.85 – 2.02 (m, 1 H), 3.10 (dd, 1 H), 3.80 (s, 3 H), 4.07 – 4.13 (m, 4 H), 5.14 (s, 2 H), 6.88 (d, 2 H), 7.31 (d, 2 H).

Step C: 4-Methoxybenzyl 2-(E and Z)-(3-(S)-(t-butyldimethylsilyloxymethyl)-4-(S)-(3-fluorophenyl)cyclopent-1-ylidenyl-3-(cyclopropyl)propionate

To a solution of 60% sodium hydride in mineral oil (0.318 g, 7.9 mmol) in THF (15 mL) was added 2-(diethoxyphosphoryl)-3-cyclopropylproprionic acid para-methoxybenzyl ester (3.7 g, 9.99 mmol) from Step B. The reaction mixture was stirred at rt for 30 min. To this solution was added a solution of (+)-*trans*-1-t-butyldimethylsilyloxymethyl-4-oxo-2-(3-fluorophenyl)cyclopentane from Example 21 Step E (0.645 g, 1.99 mmol) in THF (5 mL). The reaction mixture was stirred at rt for 2 days, diluted with diethyl ether (20 mL), poured into water (50 mL) and extracted three times with diethyl ether (3 x 20 mL). The organic layers were combined, washed with brine (50 mL), dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue (3.7 g) was purified by FC (5% ethyl acetate in hexanes) to afford the title compound as a 1 : 1 mixture of E : Z double bond isomers (0.398 g) as an oil. ^{1}H NMR ($CDCl_3$): δ -0.02 – 0.03 (br s, 6 H), 0.10 – 0.14 (m, 2 H), 0.39 (br s, 2 H), 0.89 (s, 9 H), 0.87 –0.91 (m, 1H), 2.19 (br s, 1 H), 2.27 – 2.31 (m, 2 H), 2.42 – 2.57 (m, 1.5 H), 2.66 – 2.85 (m, 2 H), 2.92 – 3.06 (m, 1 H), 3.14 – 3.17 (m, 0.5 H), 3.34 – 3.37 (m, 1 H), 3.41 –3.46 (m, 1 H), 3.82 (s, 3 H), 5.13 (s, 1 H), 5.17 (s, 1 H), 6.89 – 7.00 (m, 5 H), 7.27 – 7.35 (m, 3 H).

Step D: 4-Methoxybenzyl 2-(E)-(3-(S)-(hydroxymethyl)-4-(S)-(3-fluorophenyl)cyclopent-1-ylidenyl-3-(cyclopropyl)propionate and 4-Methoxybenzyl 2-(Z)-(3-(S)-(hydroxymethyl)-4-(S)-(3-fluorophenyl)cyclopent-1-ylidenyl-3-(cyclopropyl)propionate

4-Methoxybenzyl 2-(E and Z)-(3-(S)-(t-butyldimethylsilyloxymethyl)-4-(S)-(3-fluorophenyl)cyclopent-1-ylidenyl-3-(cyclopropyl)propionate from Step C (0.398 g, 0.74 mmol) in THF (8 mL) was added a 1.0 M solution of tetrabutylammonium fluoride in THF (1.1 mL, 1.1 mmol) and the reaction mixture was stirred at rt for 12 h. The reaction mixture was diluted with ethyl acetate, poured into 5% aqueous HCl solution, extracted three times with ethyl acetate, combined organic layers, washed with brine, dried over sodium sulfate and concentrated. The residue was purified by prep TLC eluting with 3% ethyl acetate in methylene chloride to afford separation of the E and Z isomers to give the higher R_f (0.108 g) and lower R_f (0.078 g) chiral title compounds. The higher R_f isomer was assigned as the E double bond isomer and the lower R_f isomer was assigned as the Z double bond isomer.

(Higher Rf isomer): ^{1}H NMR (C_6D_6): δ 0.20 – 0.30 (m, 2 H), 0.38 – 0.41 (m, 2 H), 0.90 – 1.00 (m, 1 H), 1.71 – 1.78 (m, 1 H), 2.10 – 2.16 (m, 1 H), 2.28 – 2.33 (m, 1 H), 2.34 – 2.41 (m, 1 H), 2.42 – 2.47 (m, 1 H), 2.55 (dd, 1 H), 2.72 – 2.79 (m, 1 H), 2.98 (dd, 1 H), 3.14 (dd, 1 H), 3.19 (s, 3 H), 3.40 (dd, 1 H), 5.12 (s, 2 H), 6.65 – 6.80 (m, 4 H), 6.83 – 6.93 (m, 1 H), 7.20 (d, 3 H).

(Lower Rf isomer): ^{1}H NMR ($CDCl_3$): δ 0.08 – 0.14 (m, 2 H), 0.34 – 0.40 (m, 2 H), 0.79 – 0.86 (m, 1 H), 2.26 – 2.28 (m, 2 H), 2.26 – 2.33 (m, 1 H), 2.55 – 2.67 (m, 2 H), 2.92 – 3.04 (m, 2 H), 3.25 (dd, 1 H), 3.48 – 3.61 (dd, 1 H), 3.62- 3.67 (dd, 1 H), 3.83 (s, 3 H), 5.16 (s, 2 H), 6.86 – 6.99 (m 4 H), 7.02 (d, 1 H), 7.03 – 7.37 (m, 3 H).

Step E: 4-Methoxybenzyl 2-(E)-(3-(S)-(formyl)-4-(S)-(3-fluorophenyl)cyclopent-1-ylidenyl-3-(cyclopropyl)propionate

To a solution of oxalyl chloride (0.020 mL, 0.029 g, 0.225 mmol) in methylene chloride (1 mL) at -70 °C was added dropwise DMSO (0.032 mL, 0.035 g, 0.45 mmol). After 10 min, a solution of the higher R_f isomer from Step D (0.019 g, 0.045 mmol) in methylene chloride (1 mL) was added dropwise. The reaction mixture was stirred at -70 °C for 45 min and then TEA (0.094 mL, 0.068 g, 0.675 mmol) was added. The reaction mixture was allowed to warm to rt for 5 min and then

diluted with methylene chloride, poured into water, and extracted three times with methylene chloride. The organic layers were combined, washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to afford the title compound which was used directly in Step F.

Step F: 4-Methoxybenzyl 2-(E)-(3-(S)-((4-(3-(benzyl)-1-ethyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-ylidenyl)-3-(cyclopropyl)propionate

To a solution of 4-methoxybenzyl 2-(E)-(3-(S)-(formyl)-4-(S)-(3-fluorophenyl)cyclopent-1-ylidenyl-3-(cyclopropyl)propionate from Step E (0.045 mmol) in 1,2-dichloroethane (1 mL) was added 4-(3-benzyl-1-ethyl-(1H)-pyrazol-5-yl)piperidine hydrochloride (0.017 g, 0.049 mmol) and DIPEA (0.016 mL, 0.012 g, 0.095 mmol). After 10 min, sodium triacetoxyborohydride (0.028 g, 0.135 mmol) was added and the reaction mixture was stirred at rt for 1 h. The reaction mixture was diluted with methylene chloride, poured into aqueous sodium bicarbonate and extracted three times with methylene chloride. The organic layers were combined, washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by prep TLC (eluting with 5% MeOH in methylene chloride) to afford the title compound (0.027 g).

Step G: 2-(E)-(3-(S)-((4-(3-(Benzyl)-1-ethyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-ylidenyl)-3-(cyclopropyl)propionic acid

4-Methoxybenzyl 2-(E)-(3-(S)-((4-(3-(benzyl)-1-ethyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-ylidenyl)-3-(cyclopropyl)propionate from Step F (0.027 g, 0.040 mmol) was taken up in 96% formic acid (1 mL) and stirred at rt for 12 h. The formic acid was removed under a stream of nitrogen. The residue was purified by ion exchange chromatography (0.5 g Varian SCX resin, eluting with 100% MeOH, then with 2.0 M NH_3/MeOH) to afford to the title compound (0.019 g).

Step H: 2-(E)-(3-(S)-((4-(3-(Benzyl)-1-ethyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-ylidenyl)-3-(cyclopropyl)propionic acid di-hydrochloride salt

2-(E)-(3-(S)-((4-(3-(benzyl)-1-ethyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-ylidenyl)-3-(cyclopropyl)propionic acid from Step G (0.019 g, 0.034 mmol) was taken up in 1:1 methylene chloride:ether (0.5 mL) and 1.0 N hydrochloric acid in diethyl ether was added (0.205 mL, 0.205 mmol). The volatiles were removed under a stream of nitrogen to give the title compound as a white solid.

HPLC/MS (ESI): 556 m/z (M + 1) Rt = 3.01 min.

EXAMPLE 39

2-(Z)-(3-(S)-((4-(3-(Benzyl)-1-ethyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-ylidenyl)-3-(cyclopropyl)propionic acid di-hydrochloride salt

Using essentially the same procedure as in Example 38, Steps A- H, but substituting the Z isomer from Step D, the title compound was obtained.

HPLC/MS (ESI): m/z 556 (M + 1) Rt = 3.33 min.

EXAMPLE 40

2-(S)-(1-(R)-3-(S)-((4-(3-(Benzyl)-1-ethyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionic acid di-hydrochloride salt

Step A: 4-methoxybenzyl 2-(S)-(1-(R)-3-(S)-hydroxymethyl-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionate

A solution of the higher R_f E double bond isomer from Example 38 from Step D (0.003 g, .007 mmol) in methylene chloride (1 mL) was hydrogenated at atmospheric pressure using (1,5-cyclooctadiene) (pyridine) (tricyclohexyl-phosphine)iridium(I) hexafluorophosphate (0.001 g) for 12 h. The volatiles were removed *in vacuo* to afford the lower R_f isomer at the 2-position of the 3-(cyclopropyl)propionate with 1,3 trans C-1 stereochemistry as the title compound.

Step B: 2-(S)-(1-(R)-3-(S)-((4-(3-(Benzyl)-1-ethyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionic acid di-hydrochloride salt

Using essentially the same procedure as in Example 21, Steps N –Q the title compound was obtained.
HPLC/MS (ESI): m/z 558 (M + 1) Rt = 3.36 min.

EXAMPLE 41

2-(R)-(1-(R)-3-(S)-((4-(3-(Benzyl)-1-ethyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionic acid di-hydrochloride salt

Using essentially the same procedure as in Example 40, Steps A - B, but substituting the lower Rf Z double bond isomer from Example 38, Step D, the title compound was obtained.
HPLC/MS (ESI): m/z 558 (M + 1) Rt = 3.28 min.

EXAMPLE 42

2-(Z)-(3-(S)-((4-(2-(4-Fluorophenylsulfonyl)eth-1-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-ylidenyl)-3-(cyclopropyl)propionic acid hydrochloride salt

Using essentially the same procedure as in Example 38, Steps C - E, but substituting the Z isomer from Step B and using 4-(2-(4-fluorophenylsulfonyl)eth-1-yl)piperidine in Step D, the title compound was obtained.
HPLC/MS (ESI): m/z 558.4 (M + 1) Rt = 3.31 min.

EXAMPLE 43

2-(Z)-(3-(S)-((4-(2-(4-Fluorophenylthio)eth-1-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-ylidenyl)-3-(cyclopropyl)propionic acid, (R and S)-sulfoxide hydrochloride salt

Using essentially the same procedure as in Example 38, Steps C - E, but substituting the Z isomer from Step B and using 4-(2-(4-fluorophenylsulfonyl)eth-1-yl)piperidine in Step D, the title compound was obtained.
HPLC/MS (ESI): m/z 542.4 (M + 1) Rt = 3.12 min.

EXAMPLE 44

2-(Z)-(3-(S)-((4-(2-(4-Fluorophenylsulfonyl)eth-1-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-ylidenyl)pentanoic acid hydrochloride salt

Using essentially the same procedure as in Example 38, Steps A - E, but substituting 4-methoxybenyl 2-(dimethyl phosphono)pentanoate in Step A, using the Z isomer from Step B, and using 4-(2-(4-fluorophenylsulfonyl)eth-1-yl)piperidine in Step D, the title compound was obtained.
HPLC/MS (ESI): m/z 546.2 (M + 1) Rt = 3.04 min.

EXAMPLE 45

2-(Z)-(3-(S)-((4-(3-(4-Methoxybenzyl)-1-ethyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-ylidenyl)pentanoic acid hydrochloride salt

Using essentially the same procedure as in Example 38, Steps A - E, but substituting 4-methoxybenyl 2-(dimethyl phosphono)pentanoate in Step A, using the Z isomer from Step B, and using 4-(3-(4-methoxybenzyl)-1-ethyl-(1H)-pyrazol-5-yl)piperidine in Step D, the title compound was obtained.
HPLC/MS (ESI): m/z 574.5 (M + 1) Rt = 3.20 min.

EXAMPLE 46

2-(E)-(3-(S)-((4-(2-(4-Fluorophenylsulfonyl)eth-1-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-ylidenyl)acetic acid hydrochloride salt

Using essentially the same procedure as in Example 38, Steps A - E, but substituting 4-methoxybenyl 2-(dimethyl phosphono)acetate in Step A, using the E isomer from Step B in Step C, and using 4-(2-(4-fluorophenylsulfonyl)eth-1-yl)piperidine in Step D, the title compound was obtained.
HPLC/MS (ESI): m/z 504.5 (M + 1) Rt = 2.53 min.

EXAMPLE 47

2-(Z)-(3-(S)-((4-(2-(4-Fluorophenylsulfonyl)eth-1-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-ylidenyl)acetic acid hydrochloride salt

Using essentially the same procedure as in Example 38, Steps A - E, but substituting 4-methoxybenyl 2-(dimethyl phosphono)acetate in Step A, using the Z isomer from Step B in Step C, and using 4-(2-(4-fluorophenylsulfonyl)eth-1-yl)piperidine in Step D, the title compound was obtained.

HPLC/MS (ESI): m/z 504.5 (M + 1) Rt = 2.69 min.

EXAMPLE 48

2-(E)-(3-(S)-((4-(3-(4-Methoxybenzyl)-1-ethyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-ylidenyl)acetic acid hydrochloride salt

Using essentially the same procedure as in Example 38, Steps A - E, but substituting 4-methoxybenyl 2-(dimethyl phosphono)acetate in Step A, using the E isomer from Step B, and using 4-(3-(4-methoxybenzyl)-1-ethyl-(1H)-pyrazol-5-yl)piperidine in Step D, the title compound was obtained.

HPLC/MS (ESI): m/z 532.6 (M + 1) Rt = 2.61 min.

EXAMPLE 49

2-(Z)-(3-(S)-((4-(3-(4-Methoxybenzyl)-1-ethyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-ylidenyl)acetic acid hydrochloride salt

Using essentially the same procedure as in Example 38, Steps A - E, but substituting 4-methoxybenyl 2-(dimethyl phosphono)acetate in Step A, using the Z isomer from Step B, and using 4-(3-(4-methoxybenzyl)-1-ethyl-(1H)-pyrazol-5-yl)piperidine in Step D, the title compound was obtained.

HPLC/MS (ESI): m/z 532.6 (M + 1) Rt = 2.77 min.

EXAMPLE 50

Based on the correlation between Examples 21 and 40 giving the same final isomer at the 2-propionic acid stereocenter and Examples 22 and 41 giving the same final isomer at the 2-propionic acid stereocenter, the stereochemical assignment for the final title compounds for Examples 21 and 23-37 were assigned the (S) stereochemistry at the 2-propionic acid center while the title product for Example 22 was assigned the (R) stereochemistry at the 2-propionic acid center.

EXAMPLE 51

Using essentially the same procedure as in Example 21, Steps O - Q, but substituting appropriate piperidine in Step O, the following title compounds were obtained.

EXAMPLE 51A

2-(S)-(1-(R)-3-(S)-((4-(3-(4-Cyanobenzyl)-1-ethyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionic acid di-hydrochloride salt

HPLC/MS (ESI): m/z 583.5 (M + 1) Rt = 3.17 min.

EXAMPLE 51B

2-(S)-(1-(R)-3-(S)-((4-(3-(Pyridin-3-yl)-1-ethyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionic acid di-hydrochloride salt

HPLC/MS (ESI): m/z 559.6 (M + 1) Rt = 2.45 min.

EXAMPLE 51C

2-(S)-(1-(R)-3-(S)-((4-(3-(2-Fluorobenzyl)-1-ethyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionic acid di-hydrochloride salt

HPLC/MS (ESI): m/z 576.5 (M + 1) Rt = 3.28 min.

EXAMPLE 51D

2-(S)-(1-(R)-3-(S)-((4-(3-(3,5-Bis-trifluoromethylbenzyl)-1-ethyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionic acid di-hydrochloride salt

HPLC/MS (ESI): m/z 694.6 (M + 1) Rt = 3.49 min.

EXAMPLE 51E

2-(S)-(1-(R)-3-(S)-((4-(3-(4-Methylsulfonylbenzyl)-1-ethyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionic acid di-hydrochloride salt

HPLC/MS (ESI): m/z 636.6 (M + 1) Rt = 2.77 min.

EXAMPLE 51F

2-(S)-(1-(R)-3-(S)-((4-(2-(4-Trifluoromethylbenzyl)thiazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionic acid di-hydrochloride salt

HPLC/MS (ESI): m/z 615.5 (M + 1) Rt = 3.28 min.

EXAMPLE 51G

2-(S)-(1-(R)-3-(S)-((4-(2-((5-Trifluoromethylpyridin-2-yl)sulfonyl)eth-1-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionic acid di-hydrochloride salt

HPLC/MS (ESI): m/z 611.4 (M + 1) Rt = 3.79 min.

EXAMPLE 51H

2-(S)-(1-(R)-3-(S)-((4-(2-(4-Benzyl)thiazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionic acid di-hydrochloride salt

HPLC/MS (ESI): m/z 547.5 (M + 1) Rt = 3.28 min.

EXAMPLE 51I

2-(S)-(1-(R)-3-(S)-((4-(3-(4-Methoxybenzyl)-1-ethyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionic acid di-hydrochloride salt

HPLC/MS (ESI): m/z 588.3 (M + 1) Rt = 3.23 min.

EXAMPLE 51J

2-(S)-(1-(R)-3-(S)-((4-(3-(3-Fluorobenzyl)-1-ethyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionic acid di-hydrochloride salt

HPLC/MS (ESI): m/z 576.5 (M + 1) Rt = 3.33 min.

EXAMPLE 51K

2-(S)-(1-(R)-3-(S)-((4-(3-(4-Chlorobenzyl)-1-ethyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionic acid di-hydrochloride salt

HPLC/MS (ESI): m/z 592.2, 594.5 (M + 1, M + 3) Rt = 3.47 min.

EXAMPLE 51L

2-(S)-(1-(R)-3-(S)-((4-(3-(3,4-Difluorobenzyl)-1-ethyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionic acid di-hydrochloride salt

HPLC/MS (ESI): m/z 594.5 (M + 1) Rt = 3.41 min.

EXAMPLE 51M

-(S)-(1-(R)-3-(S)-((4-(3-Benzylpryidin-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionic acid di-hydrochloride salt

HPLC/MS (ESI): m/z 541.5 (M + 1) Rt = 2.69 min.

EXAMPLE 51N

2-(S)-(1-(R)-3-(S)-((4-(3-(Pyridin-3-ylmethyl)-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionic acid tri-hydrochloride salt

HPLC/MS (ESI): m/z 531.5 (M + 1) Rt = 2.37 min.

EXAMPLE 51O

2-(S)-(1-(R)-3-(S)-((4-(2-Benzyl-4-methylthiazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionic acid di-hydrochloride salt

HPLC/MS (ESI): m/z 561.5 (M + 1) Rt = 3.17 min.

EXAMPLE 51P

2-(S)-(1-(R)-3-(S)-((4-(2-Benzyl-4-ethylthiazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionic acid di-hydrochloride salt

HPLC/MS (ESI): m/z 575.5 (M + 1) 3.33 min.

EXAMPLE 51Q

2-(S)-(1-(R)-3-(S)-((4-(Imidazo[1,2-a]pyridin-3-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionic acid di-hydrochloride salt

HPLC/MS (ESI): m/z 490.5 (M + 1) Rt = 2.37 min.

EXAMPLE 51R

2-(S)-(1-(R)-3-(S)-((4-(3-(4-Trifluoromethylbenzyl)-1-ethyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionic acid di-hydrochloride salt

HPLC/MS (ESI): m/z 626.2 (M + 1) Rt = 3.57 min.

EXAMPLE 51S

2-(S)-(1-(R)-3-(S)-((4-(3-(4-Ethoxybenzyl)-1-ethyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionic acid di-hydrochloride salt

HPLC/MS (ESI): m/z 605.2 (M + 1) Rt = 2.06 min.

EXAMPLE 51T

2-(S)-(1-(R)-3-(S)-((4-(3-(Cyclohexylmethyl)-1-ethyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionic acid di-hydrochloride salt

HPLC/MS (ESI): m/z 564.5 (M + 1) Rt = 2.04 min.

EXAMPLE 51U

2-(S)-(1-(R)-3-(S)-((4-(3-(4-Trifluoromethoxybenzyl)-1-ethyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionic acid di-hydrochloride salt

HPLC/MS (ESI): m/z 642.4 (M + 1) Rt = 2.19 min.

EXAMPLE 51V

2-(S)-(1-(R)-3-(S)-((4-(3-(4-Nitrobenzyl)-1-ethyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionic acid di-hydrochloride salt

HPLC/MS (ESI): m/z 603.5 (M + 1) Rt = 2.02 min.

EXAMPLE 51W

2-(S)-(1-(R)-3-(S)-((4-(2-(4-Fluorobenzyl)-4-ethylthiazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionic acid di-hydrochloride salt

HPLC/MS (ESI): m/z 593.7 (M + 1) Rt = 2.10 min.

EXAMPLE 51X

2-(S)-(1-(R)-3-(S)-((4-(2-(4-Chlorobenzyl)-4-ethylthiazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionic acid di-hydrochloride salt

HPLC/MS (ESI): m/z 609, 611 (M + 1, M + 3) Rt = 2.21 min.

EXAMPLE 51Y

2-(S)-(1-(R)-3-(S)-((4-(2-(4-Trifluoromethylbenzyl)-4-ethylthiazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionic acid di-hydrochloride salt

HPLC/MS (ESI): m/z 643.6 (M + 1) Rt = 2.26 min.

EXAMPLE 51Z

2-(S)-(1-(R)-3-(S)-((4-(3-(4-Isopropylbenzyl)-1-ethyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionic acid di-hydrochloride salt

HPLC/MS (ESI): m/z 600.5 (M + 1) Rt = 2.28 min.

EXAMPLE 51AA

2-(S)-(1-(R)-3-(S)-((4-(3-(4-Methylbenzyl)-1-ethyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionic acid di-hydrochloride salt

HPLC/MS (ESI): m/z 572.5 (M + 1) Rt = 2.12 min.

EXAMPLE 51BB

2-(S)-(1-(R)-3-(S)-((4-(3-(4-methylcyclohexylmethyl)-1-ethyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionic acid di-hydrochloride salt

HPLC/MS (ESI): m/z 578.7 (M + 1) Rt = 2.21 min.

EXAMPLE 51CC

2-(S)-(1-(R)-3-(S)-((4-(2-(Pyridin-3-yl)-4-ethylthiazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionic acid tri-hydrochloride salt

HPLC/MS (ESI): m/z 576.7 (M + 1) Rt = 1.66 min.

EXAMPLE 51DD

2-(S)-(1-(R)-3-(S)-((4-(3-(4-Difluoromethoxybenzyl)-1-ethyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)propionic acid di-hydrochloride salt

HPLC/MS (ESI): m/z 624.4 (M + 1) Rt = 2.13 min.

EXAMPLE 52

Using essentially the same procedure as in Example 21, Steps L - Q, but substituting bromomethylcyclobutane in Step L, using the required lower isomer from Step M, and the appropriate piperidine in Step O, the following title compounds were obtained.

EXAMPLE 52A

2-(S)-(1-(R)-3-(S)-((4-(3-Benzyl-1-ethyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclobutyl)propionic acid di-hydrochloride salt

HPLC/MS (ESI): m/z 572.6 (M + 1) Rt = 3.95 min.

EXAMPLE 52B

2-(S)-(1-(R)-3-(S)-((4-(3-Benzyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclobutyl)propionic acid di-hydrochloride salt

HPLC/MS (ESI): m/z 544.5 (M + 1) Rt = 3.81 min.

EXAMPLE 52C

2-(S)-(1-(R)-3-(S)-((4-(2-(4-Fluorophenylsulfonyl)eth-1-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclobutyl)propionic acid di-hydrochloride salt

HPLC/MS (ESI): m/z 574.5 (M + 1) Rt = 3.87 min.

EXAMPLE 52D

2-(S)-(1-(R)-3-(S)-((4-(3-(4-Methoxybenzyl)-1-ethyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclobutyl)propionic acid di-hydrochloride salt

HPLC/MS (ESI): m/z 602.5 (M + 1) Rt = 3.41 min.

EXAMPLE 52E

2-(S)-(1-(R)-3-(S)-((4-(3-(4-Trifluoromethylbenzyl)-1-ethyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclobutyl)propionic acid di-hydrochloride salt

HPLC/MS (ESI): m/z 640.6 (M + 1) Rt = 3.71 min.

EXAMPLE 52F

2-(S)-(1-(R)-3-(S)-((4-(3-(4-Cyanobenzyl)-1-ethyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclobutyl)propionic acid di-hydrochloride salt

HPLC/MS (ESI): m/z 597.4 (M + 1) Rt = 2.08 min.

EXAMPLE 52G

2-(S)-(1-(R)-3-(S)-((4-(3-(4-Methylsulfonylbenzyl)-1-ethyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclobutyl)propionic acid di-hydrochloride salt

HPLC/MS (ESI): m/z 650.3 (M + 1) Rt = 1.99 min.

EXAMPLE 53

Using essentially the same procedure as in Example 21, Steps L - Q, but substituting bromomethylcyclobutane in Step L, using the higher isomer from Step M, and the appropriate piperidine in Step O, the following title compounds were obtained.

2-(R)-(1-(R)-3-(S)-((4-(4-Fluorophenylsulfonyl)eth-1-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclobutyl)propionic acid hydrochloride salt

HPLC/MS (ESI): m/z 574.5 (M + 1) Rt = 3.87 min.

EXAMPLE 54

2-(S or R)-(1-(R)-3-(S)-((4-(3-(4-Trifluoromethylbenzyl)-1-ethyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)-2-hydroxypropionic acid di-hydrochloride salt

Step A: 4-Methoxybenzyl 2-(R and S)-(1-(R)-3-(S)-t-butyldimethylsilyloxymethyl-4-(S)-(3-fluorophenylcyclopent-1-yl))-3-(cyclopropyl)-2-hydroxypropionate

To a solution of 4:1 THF/hexamethylphosphoramide (32 mL) at -78 °C was added 1.5 M lithium diisopropylamide mono(tetrahydrofuran) solution in cyclohexane (1.5 mL, 2.28 mmol). To this solution was then added a solution of 4-methoxybenzyl 2-(R and S)-(1-(R)-3-(S)-t-butyldimethylsilyloxymethyl-4-(S)-(3-fluorophenylcyclopent-1-yl)-3-(cyclopropyl)propionate from Example 21 Step L (0.821 g, 1.52 mmol) in THF (20 mL) and the reaction mixture was stirred at -78 °C for 40 min. To this solution was then added a solution of (+)- ((camphoryl)sulfonyl) oxaziridine (0.696 g, 3.04 mmol) in THF (15 mL). The reaction mixture was stirred for 1.5 h and was then allowed to warm to rt for 20 min. The reaction mixture was diluted with diethyl ether, poured into saturated ammonium chloride and extracted three times with diethyl ether. The organic layers were combined, washed three times with water and once with brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by FC (3.5 - 6% ethyl acetate in hexanes) to afford the title product (0.030 g) as an oil.

^{1}H NMR ($CDCl_3$): δ –0.01 – 0.00 (m, 6 H), 0.01 – 0.10 (m, 2 H), 0.30 – 0.40 (m, 2 H), 0.70 – 0.80 (m, 1 H), 0.90 (s, 9 H), 1.20 – 1.42 (m, 2 H), 1.44 – 1.54 (m, 0.5 H), 1.56 – 1.60 (m, 0.5 H), 1.60 – 1.81 (m, 2 H), 1.80 – 1.95 (m, 1 H), 2.10 – 2.17 (m, 1 H), 2.19 – 2.32 (m, 1 H), 2.34 – 2.45 (m, 0.5 H), 2.70 – 2.82 (m, 0.5 H), 3.32 – 3.59 (m, 2 H), 3.78 – 3.92 (m, 3 H), 5.13 – 5.25 (m, 2 H), 6.80 – 7.10 (m, 5 H), 7.15 – 7.40 (m, 3 H).

Step B: 4-Methoxybenzyl 2-(S or R)-(1-(R)-3-(S)-((4-(3-(4-trifluoromethylbenzyl)-1-ethyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)-2-hydroxypropionate

Using 4-methoxybenzyl 2-(R and S)-(1-(R)-3-(S)-t-butyldimethylsilyloxymethyl-4-(S)-(3-fluorophenylcyclopent-1-yl))-3-(cyclopropyl)-2-hydroxypropionate from Step A and essentially the same procedure as in Example 21 Steps M-O the title compound was prepared from the higher Rf isomer following separation of the diastereomers after Step M using FC (10% ethyl acetate in methylene chloride). The stereochemistries were not assigned. In Step O 4-(3-(4-

trifluoromethylbenzyl)-1-ethyl-(1H)-pyrazol-5-yl)piperidine hydrochloride was substituted.

Step C: 2-(S or R)-(1-(R)-3-(S)-((4-(3-(4-Trifluoromethylbenzyl)-1-ethyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)-2-hydroxypropionic acid di-hydrochloride salt.

A solution of from 4-methoxybenzyl 2-(S or R)-(1-(R)-3-(S)-((4-(3-(4-trifluoromethylbenzyl)-1-ethyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)-2-hydroxypropionate from Step B (0.015 g, 0.19 mmol) in methanol (4 mL) was hydrogenated at atmospheric pressure using palladium on carbon (0.005 g) for 3 d. The reaction mixture was filter and the volatiles were removed *in vacuo* to afford a crude residue (0.015 g) which was purified by prep TLC (eluting with 85/15/1/1 methylene chloride/methanol/ammonia hydroxide/water to afford the acid (0.005 g) which was taken up in 1:1 methylene chloride:ether (0.5 mL) and 1.0 N hydrochloride acid in diethyl ether was added (0.022 mL, 0.022 mmol). The volatiles were removed under a stream of nitrogen to give the title compound as a white solid.

HPLC/MS (ESI): m/z 642 (M + 1) Rt = 2.15 min.

EXAMPLE 54A

2-(R or S)-(1-(R)-3-(S)-((4-(3-(4-Trifluoromethylbenzyl)-1-ethyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-3-(cyclopropyl)-2-hydroxypropionic acid di-hydrochloride salt

Using essentially the same procedure as in Example 54, Steps A-C, but substituting the lower Rf isomer following separation of the diastereomers after Step M, the title compound was obtained.

HPLC/MS (ESI): m/z 642 (M + 1) Rt = 3.01 min.

EXAMPLE 55

2-(S or R)-(1-(R or S)-3-(S)-((4-(3-Benzyl)-1-ethyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl-3-(cyclopropyl)-2-fluoropropionic acid di-hydrochloride salt

Step A: Ethyl (E and Z)-3-(S)-t-butyldimethylsilyloxymethyl-4-(S)-phenylcyclopent-1-ylidene-2-fluoroacetate

To a solution of 60% sodium hydride in mineral oil (0.028 g, 0.709 mmol) in THF (2 mL) was added 2-fluoro-2-phosphonoacetic acid triethyl ester (0.180 mL, 0.89 mmol). The reaction mixture was stirred at rt for 30 min. To this solution was then added a solution of (+)-*trans*-3-t-butyldimethylsilyloxymethyl-4-phenylcyclopentan-1-one from Example 11 Step G (0.054 g, 0.17 mmol) in THF (2 mL). The reaction mixture was stirred at rt for 2 d, diluted with diethyl ether, poured into water and extracted three times with diethyl ether. The organic layers were combined, washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by prep TLC (eluting with 3% ethyl acetate in hexanes) to afford the title compound as a 1 : 1 mixture of E : Z double bond isomers (0.053 g) as an oil.

^{1}H NMR ($CDCl_3$): δ 0.00 (s, 6 H), 0.90 (s, 9 H), 0.35 (t, 1.5 H), 0.39 (t, 1.5 H), 2.20 – 2.34 (m, 1 H), 2.54 – 2.63 (m, 0.5 H), 2.66 – 2.76 (m, 1 H), 2.78 – 2.87 (m, 0.5 H), 2.89 – 2.96 (m, 0.5 H), 3.00 – 3.18 (m, 2 H), 3.30 – 3.38 (dd, 0.5 H), 3.43 – 3.49 (m, 1 H), 3.62 (dt, 1 H), 7.22 – 7.27 (m, 3 H), 7.31 – 7.36 (m, 2 H).

Step B: Ethyl (1-(R and S)-3-(S)-hydroxymethyl-4-(S)-phenylcyclopent-1-yl)-2-(S and R)-fluoroacetate

A solution of ethyl (E and Z)-3-(S)-t-dimethylsilyloxymethyl-4-(S)-phenylcyclopent-1-ylidene-2-fluoroacetate from Step A (0.053 g, 0.135 mmol) in ethanol (3 mL) was hydrogenated at 50 psi using palladium on carbon (0.010 g) for 28 h. The reaction mixture was filtered through Celite and the volatiles were removed *in vacuo* to afford the title compound (0.027 g).

^{1}H NMR ($CDCl_3$): δ –0.08 – 0.01 (m, 6 H), 0.90 (s, 9 H), 1.30 – 1.40 (m, 3 H), 1.79 – 2.00 (m, 2 H), 2.01 – 2.25 (m, 3 H), 2.55 – 2.82 (m, 1 H), 2.85 – 2.95 (m, 1 H), 3.39 – 3.46 (m, 1 H), 3.54 – 3.60 (m, 1 H), 4.23 – 4.32 (m, 2 H), 4.80 – 4.99 (m, 1 H), 7.18 – 7.27 (m, 3 H), 7.28 – 7.33 (m, 2 H).

Step C: 2-(S or R)-(1-(R or S)-3-(S)-((4-(3-Benzyl)-1-ethyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl-3-(cyclopropyl)-2-fluoropropionic acid di-hydrochloride salt

Using essentially the same procedure as Example 21, Steps J – Q, the title compound was prepared (0.009 g). Following Step M, the diastereomers were separated by FC (5% ethyl acetate in hexanes) to afford an upper Rf isomer (0.021 g) and a lower Rf isomer (0.033 g). The upper Rf isomer was then separated further using chiral prep HPLC on a 2 cm x 25 cm Chiracel OD column eluting with 30% isopropanol in hexanes and afforded a first eluting peak Rt = 13.7 min (0.008g) and a second eluting peak Rt = 18.7 min (0.009 g). The lower Rf isomer was also separated further using chiral prep HPLC on a 2 cm x 25 cm Chiracel OJ column eluting with 40% ethanol in hexanes and afforded a first eluting peak Rt = 33.8 min (0.007 g) and a second eluting peak Rt = 39.8 (0.013 g). No stereochemistries were assigned. This title compound was derived from the upper Rf isomer following FC and the first eluting peak following chiral HPLC.
HPLC/MS (ESI): m/z 558 (M + 1) Rt = 3.01 min.

EXAMPLE 55A

2-(R or S)-(1-(R or S)-3-(S)-((4-(3-Benzyl)-1-ethyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl-3-(cyclopropyl)-2-fluoropropionic acid di-hydrochloride salt

Using essentially the same procedure as Example 55, Steps A-C, the title compound was prepared (0.011 g). The title compound was derived from the upper Rf isomer following FC and the second eluting peak following chiral HPLC.
HPLC/MS (ESI): m/z 558 (M + 1) Rt = 3.01 min.

EXAMPLE 55B

2-(R or S)-(1-(S or R)-3-(S)-((4-(3-Benzyl)-1-ethyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl-3-(cyclopropyl)-2-fluoropropionic acid di-hydrochloride salt

Using essentially the same procedure as Example 55, Steps A-C, the title compound was prepared (0.008 g). The title compound was derived from the lower Rf isomer following FC and the first eluting peak following chiral HPLC
HPLC/MS (ESI): m/z 558 (M + 1) Rt = 3.23 min.

EXAMPLE 55C

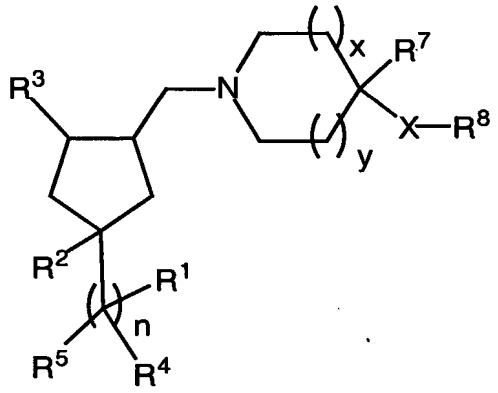
2-(S or R)-(1-(S or R)-3-(S)-((4-(3-Benzyl)-1-ethyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl-3-(cyclopropyl)-2-fluoropropionic acid di-hydrochloride salt

Using essentially the same procedure as Example 55, Steps A-Cthe title compound was prepared (0.014 g). The title compound was derived from the lower Rf isomer following FC and the second eluting peak following chiral HPLC
HPLC/MS (ESI): m/z 558 (M + 1) Rt = 3.23 min.

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made without departing from the spirit and scope of the invention. For example, effective dosages other than the particular dosages as set forth herein above may be applicable as a consequence of variations in the responsiveness of the mammal being treated for any of the indications with the compounds of the invention indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compounds selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be defined by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

WHAT IS CLAIMED IS:

1. A compound of the formula I:



I

wherein:

X is selected from: -(C_{0-6} alkyl)-Y-(C_{0-6} alkyl)-,
-(C_{0-6} alkyl)-C_{3-8} cycloalkyl-(C_{0-6} alkyl)-,
C_{2-10} alkenyl, and C_{2-10} alkynyl,
where the alkyl is unsubstituted or substituted with 1-7 substituents where the substituents are independently selected from:
(a) halo,
(b) hydroxy,
(c) -O-C_{1-3} alkyl, and
(d) trifluoromethyl,

and where Y is selected from:
a single bond, -O-, -SO_2-, -NR^{10}-, -NR^{10}-SO_2-, -SO_2-NR^{10}-,
-S-, and -SO-,

and where R^{10} is independently selected from: hydrogen, C_{1-6} alkyl, benzyl, phenyl, and C_{1-6} alkyl-C_{3-6} cycloalkyl,
which is unsubstituted or substituted with 1-3 substituents where the substituents are independently selected from: halo, C_{1-3} alkyl, C_{1-3} alkoxy and trifluoromethyl;

R^1 is selected from:

(1) $-CO_2H$,
(2) $-NO_2$,
(3) -tetrazolyl,
(4) -hydroxyisoxazole,
(5) $-SO_2NHCO-(C_{0-3}$ alkyl)$-R^9$, and
(6) $-P(O)(OH)_2$;

where R^9 is independently selected from: hydrogen, C_{1-10} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkyl-C_{3-6} cycloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, benzyl or phenyl, which is unsubstituted or substituted with 1-3 substituents where the substituents are independently selected from: halo, C_{1-3} alkyl, C_{1-3} alkoxy and trifluoromethyl,

R^2 is selected from:
(1) hydrogen, and
(2) hydroxy;

R^3 is selected from the group consisting of:
phenyl and heterocycle,
which is unsubstituted or substituted with 1-7 substituents where the substituents are independently selected from:
(a) halo,
(b) trifluoromethyl,
(c) hydroxy,
(d) C_{1-3} alkyl,
(e) $-O-C_{1-3}$ alkyl,
(f) $-CO_2R^9$,
(g) $-NR^9R^{10}$, and
(h) $-CONR^9R^{10}$;

R^4 and R^5 are independently selected from:
hydrogen, hydroxy, fluoro, C_{1-10} alkyl, C_{3-8} cycloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, phenyl, -(C_{1-6} alkyl)-phenyl, -(C_{1-6} alkyl)-C_{3-8} cycloalkyl, naphthyl, biphenyl, and heterocycle,

which is unsubstituted or substituted with 1-7 of R^{11} where R^{11} is independently selected from:

(a) halo,
(b) trifluoromethyl,
(c) hydroxy,
(d) C_{1-3} alkyl,
(e) -O-C_{1-3} alkyl,
(f) $-CO_2R^9$, and
(g) $-CONR^9R^{10}$,

or where R^4 and R^5 may be joined together to form a 3-8 membered saturated ring which may be unsubstituted or substituted with 1-7 of R^{11},
or where, if n is 1, R^2 and R^4 may be joined together to form a double bond;

R^7 is selected from:

(1) hydrogen,
(2) C_{1-6} alkyl, which is unsubstituted or substituted with 1-4 substituents where the substituents are independently selected from: hydroxy, cyano, and halo,
(3) hydroxy, and
(4) halo;

R^8 is selected from:

hydrogen, C_{3-8} cycloalkyl, phenyl, naphthyl, biphenyl, and heterocycle, which is unsubstituted or substituted with 1-7 of R^{12} where R^{12} is independently selected from:

(a) halo,
(b) cyano,
(c) hydroxy,
(d) C_{1-6} alkyl, which is unsubstituted or substituted with 1-5 of R^{13} where R^{13} is independently selected from: halo, cyano, hydroxy, C_{1-6} alkoxy, $-CO_2H$, $-CO_2(C_{1-6}$ alkyl), trifluoromethyl, and $-NR^9R^{10}$,
(e) -O-C_{1-6} alkyl, which is unsubstituted or substituted with 1-5 of R^{13},

(f) $-CF_3$,
(g) $-CHF_2$,
(h) $-CH_2F$,
(i) $-NO_2$,
(j) C_{0-6} alkyl-phenyl or C_{0-6} alkyl-heterocycle, which is unsubstituted or substituted with 1-7 substituents where the substituents are independently selected from:
(i) halo,
(ii) hydroxy,
(iii) C_{1-6} alkyl,
(iv) $-O-C_{1-6}$ alkyl,
(v) $-CF_3$,
(vi) $-OCF_3$,
(vii) $-NO_2$,
(viii) -CN,
(ix) $-SO_2-C_{1-6}$ alkyl,
(x) $-CO_2R^9$,
(xi) $-NR^9R^{10}$,
(xii) $-CONR^9R^{10}$,
(xiii) $-SO_2-NR^9R^{10}$, and
(xiv) $-NR^9-SO_2-R^{10}$;
(k) $-CO_2R^9$,
(l) tetrazolyl,
(m) $-NR^9R^{10}$,
(n) $-NR^9-COR^{10}$,
(o) $-NR^9-CO_2R^{10}$,
(p) $-CO-NR^9R^{10}$,
(q) $-OCO-NR^9R^{10}$,
(r) $-NR^9CO-NR^9R^{10}$,
(s) $-S(O)_m-R^9$, wherein m is an integer selected from 0, 1 and 2,
(t) $-S(O)_2-NR^9R^{10}$,
(u) $-NR^9S(O)_2-R^{10}$, and
(v) $-NR^9S(O)_2-NR^9R^{10}$;

n is an integer selected from 1, 2, 3 and 4;
x is an integer selected from 0, 1 and 2, and y is an integer selected from 0, 1 and 2, with the proviso that the sum of x and y is 2;

and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

2. A compound of Claim 1, wherein R^1 is selected from:
(1) $-CO_2H$,
(2) $-NO_2$,
(3) -tetrazolyl,
(4) -hydroxyisoxazole, and
(5) $-P(O)(OH)_2$; and

each R^9 is independently selected from: hydrogen, C_{1-6} alkyl, C_{5-6} cycloalkyl, benzyl or phenyl, which is unsubstituted or substituted with 1-3 substituents where the substituents are independently selected from: halo, C_{1-3} alkyl, C_{1-3} alkoxy and trifluoromethyl;

and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

3. A compound of Claim 1, wherein R^1 is selected from:
(1) $-CO_2H$, and
(2) -tetrazolyl;

and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

4. A compound of Claim 3, wherein R^1 is $-CO_2H$;

and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

5. A compound of Claim 1, wherein R^3 is selected from the group consisting of phenyl and thienyl, which may be unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from:
(a) halo,

(b) trifluoromethyl,
(c) hydroxy,
(d) C_{1-3} alkyl, and
(e) -O-C_{1-3} alkyl;

and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

6. A compound of Claim 5, wherein R^3 is unsubstituted phenyl, (3-fluoro)phenyl or 3-thienyl;

and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

7. A compound of Claim 1, wherein R^2 is hydrogen;

and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

8. A compound of Claim 1, wherein R^4 is hydrogen or C_{1-6} alkyl;

and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

9. A compound of Claim 1, wherein R^5 is selected from: hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{1-6} alkyl-C_{3-8} cycloalkyl, and phenyl;

and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

10. A compound of Claim 9, wherein R^5 is selected from: hydrogen, methyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, cyclohexyl, -CH_2-cyclopropyl, -CH_2-cyclobutyl and phenyl;

and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

11. A compound of Claim 1, wherein R^7 is hydrogen, fluoro, hydroxy or C_{1-6} alkyl;

12. A compound of Claim 11, wherein R^7 is hydrogen;

and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

13. A compound of Claim 1, wherein X is
-(C_{0-2} alkyl)-Y-(C_{0-2} alkyl)-,
where the alkyl is unsubstituted or substituted with 1-4 substituents where the substituents are independently selected from:
(a) halo,
(b) hydroxy,
(c) -O-C_{1-3} alkyl, and
(d) trifluoromethyl,
and where Y is selected from:
a single bond, -O-, -SO_2-, -NR^{10}-, -S-, and -SO-,
where R^{10} is independently selected from: hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, benzyl, phenyl, and C_{1-6} alkyl-C_{3-6} cycloalkyl, which is unsubstituted or substituted with 1-3 substituents where the substituents are independently selected from: halo, C_{1-3} alkyl, C_{1-3} alkoxy and trifluoromethyl;

and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

14. A compound of Claim 13, wherein X is selected from:
(1) a single bond,
(2) -CH_2CH_2-,
(3) -$CH_2CH_2CH_2$-,
(4) -CH_2CH_2-CF_2-,
(5) -CH_2CH_2-SO_2-, and
(6) -CH_2CH_2-SO- ;

and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

15. A compound of Claim 1, wherein R^8 is selected from phenyl, imidazopyridyl, imidazolyl, oxazolyl, pyrazolyl, pyridyl, thiazolyl, tetrahydroindazolyl, tetrahydroimidazopyridyl, and tetrahydropyrazolopyridyl;

which is unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from:

(a) halo,
(b) cyano,
(c) $-NO_2$,
(d) $-CF_3$,
(e) $-CHF_2$,
(f) $-CH_2F$,
(h) C_{1-6} alkyl,
(i) C_{1-3} alkyl-phenyl or C_{1-3} alkyl-pyridyl, which is unsubstituted or substituted with 1-4 substituents where the substituents are independently selected from:
  (i) halo,
  (ii) C_{1-6} alkyl,
  (iii) $-O-C_{1-6}$ alkyl,
  (iv) $-CF_3$,
  (vi) $-OCF_3$,
  (vii) -CN, and
(j) $-O-C_{1-6}$ alkyl;

and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

16. A compound of Claim 15, wherein R^8 is selected from 5-(3-benzyl)pyrazolyl, 5-(1-methyl-3-benzyl)pyrazolyl, 5-(1-ethyl-3-benzyl)pyrazolyl, 5-(2-benzyl)thiazolyl, 5-(2-benzyl-4-methyl)thiazolyl, and 5-(2-benzyl-4-ethyl)thiazolyl);

and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

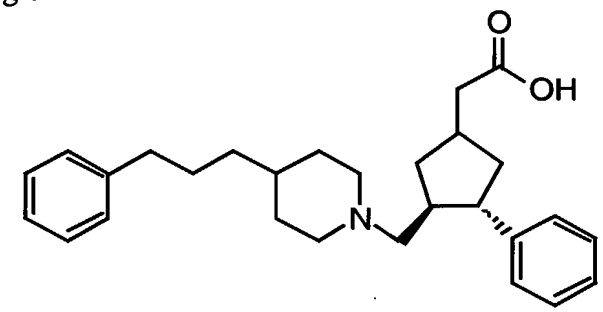
17. A compound of Claim 1, wherein n is an integer which is 1 or 2;

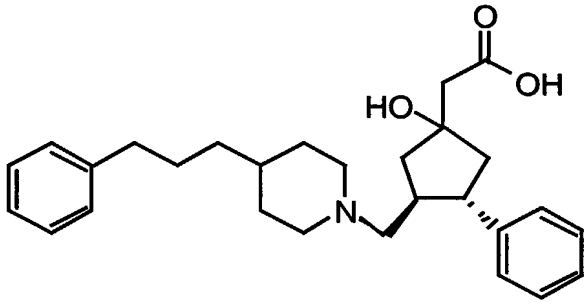
and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

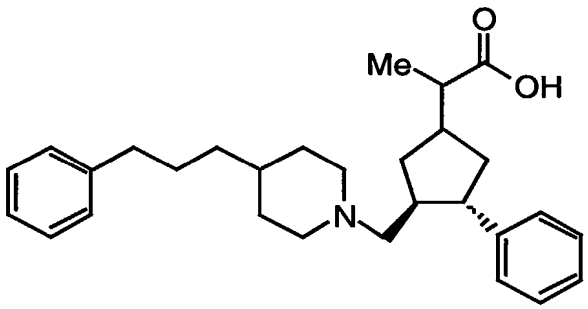
18. A compound of Claim 1, wherein x is an integer which is 1 and y is an integer which is 1;

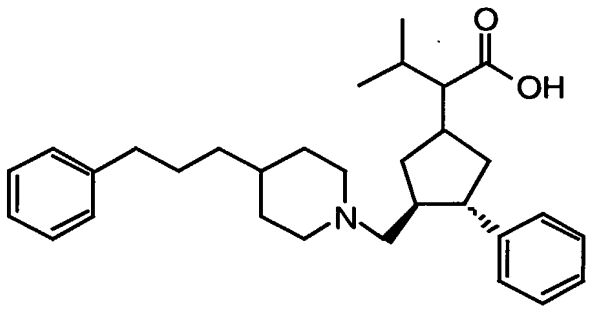
and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

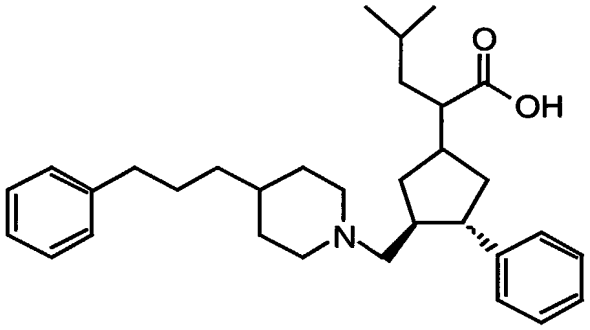
19. A compound of Claim 1, which is a compound selected from the group consisting of

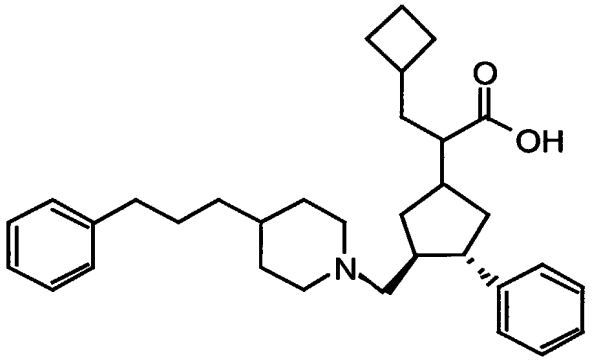












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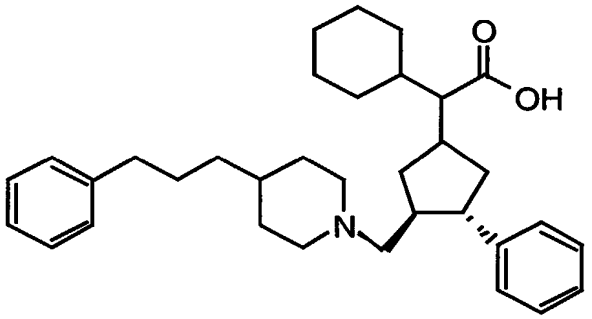

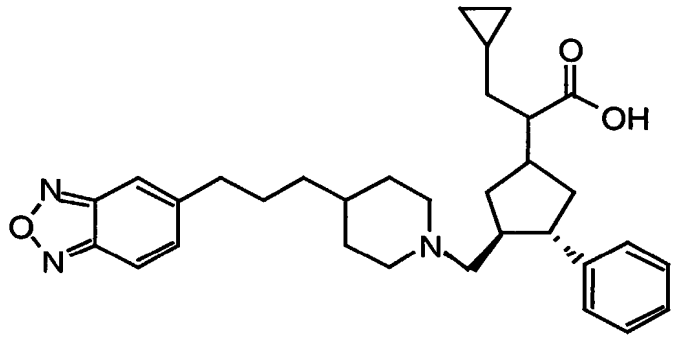

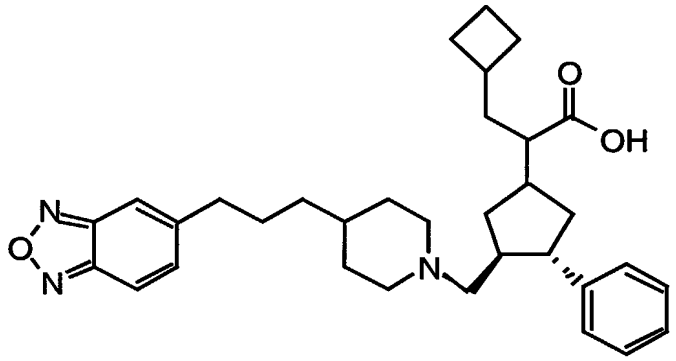

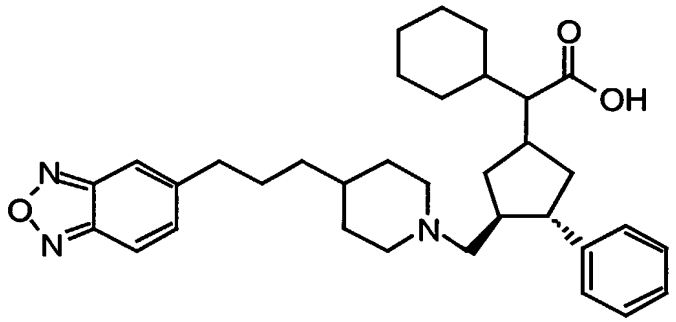

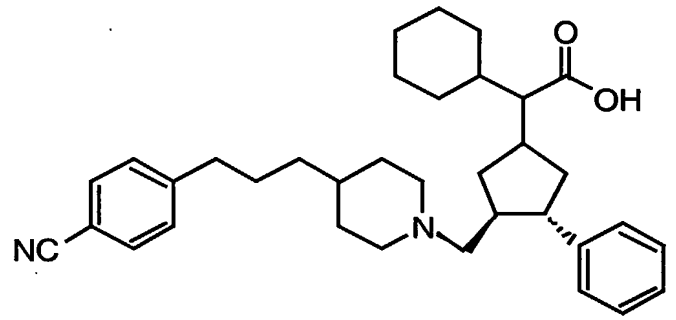

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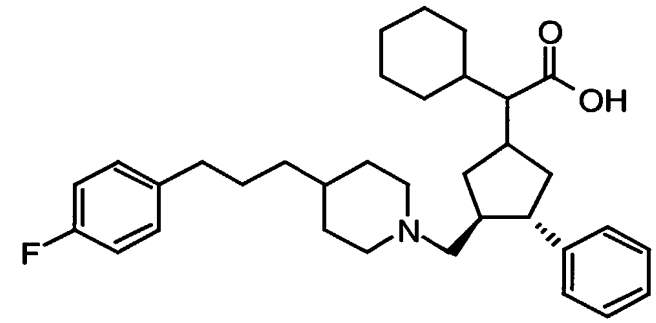

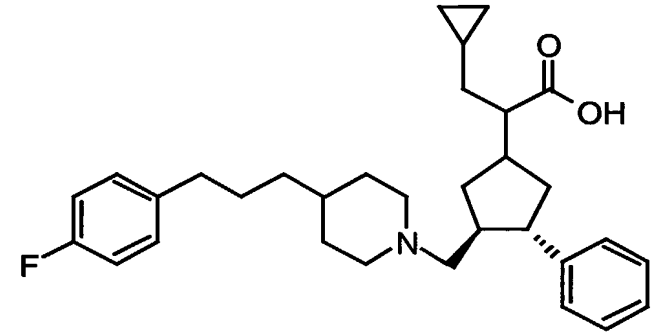

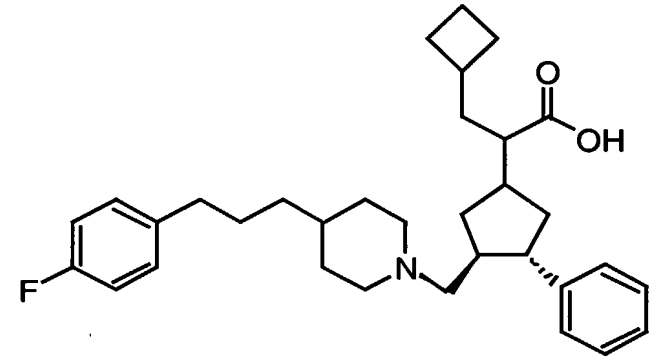

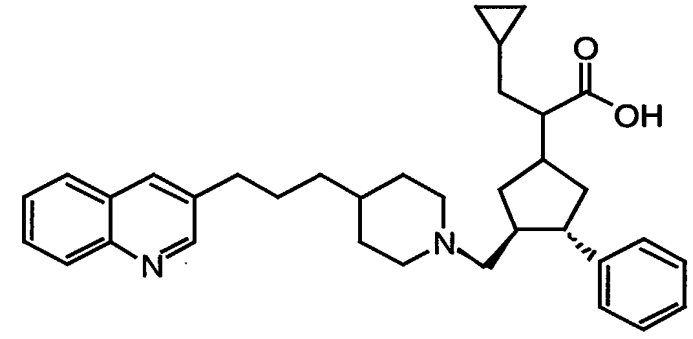

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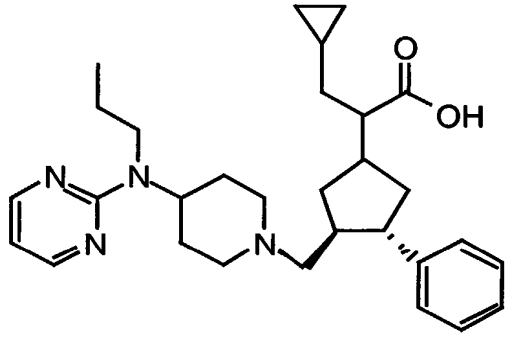

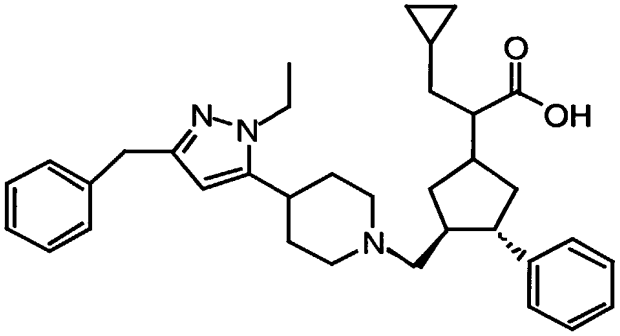

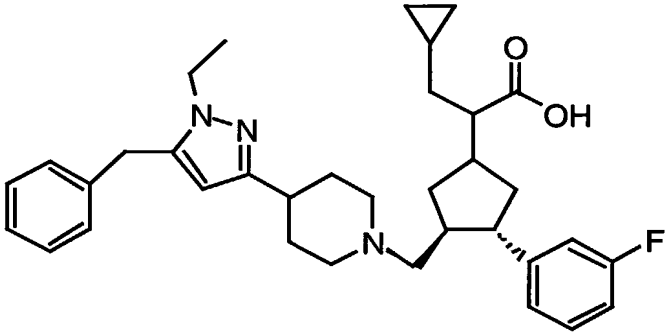

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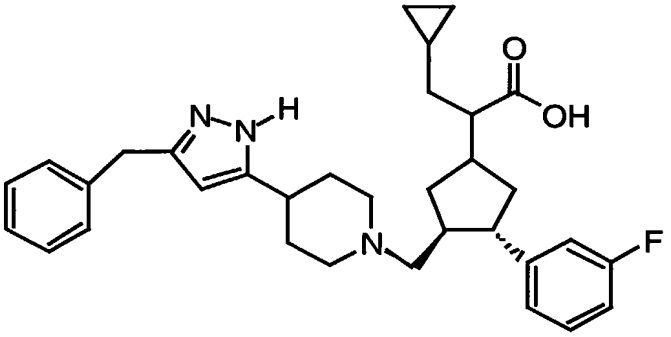

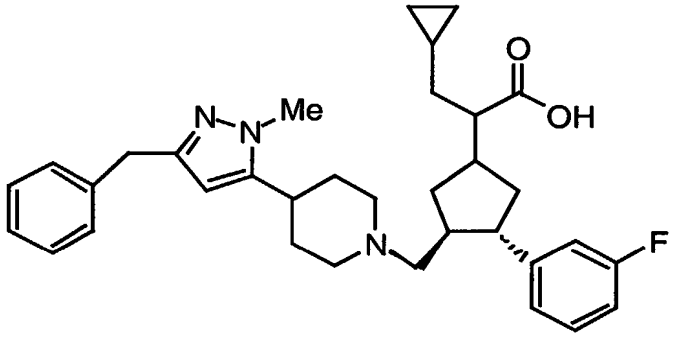

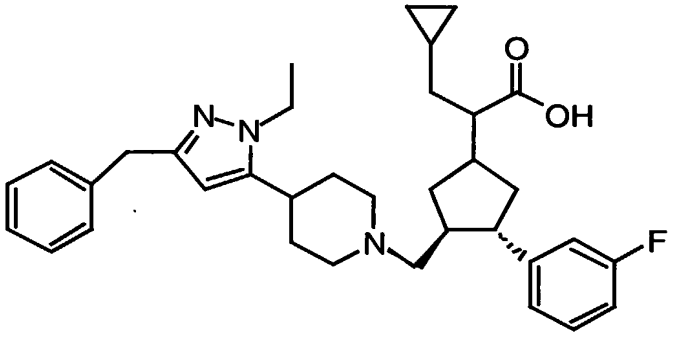

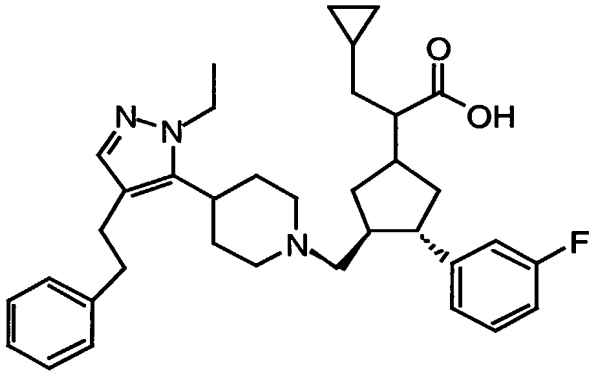

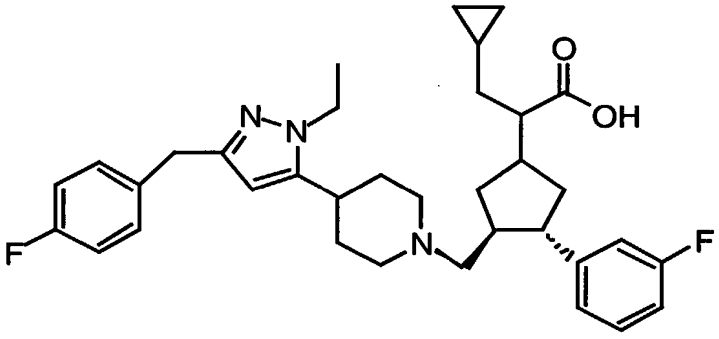

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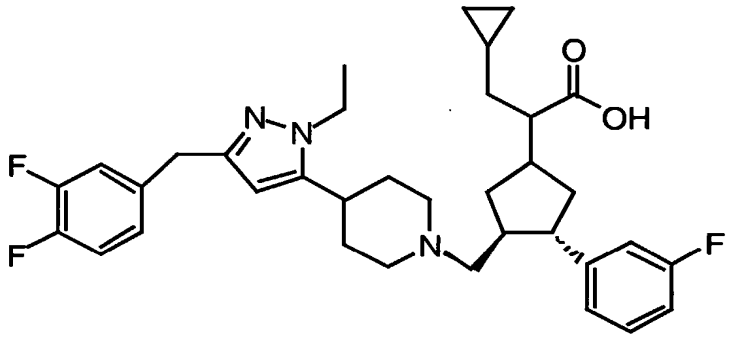
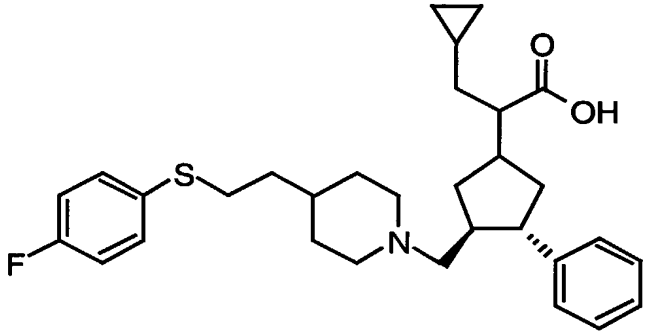
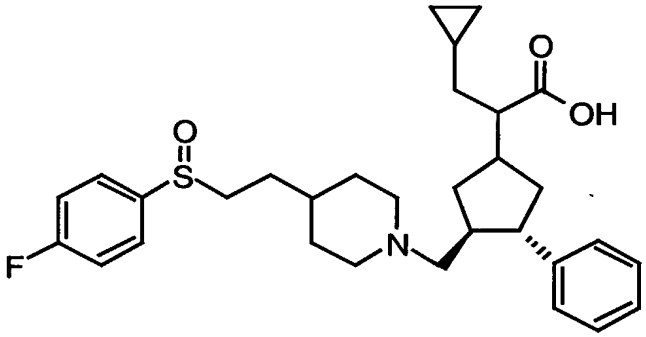
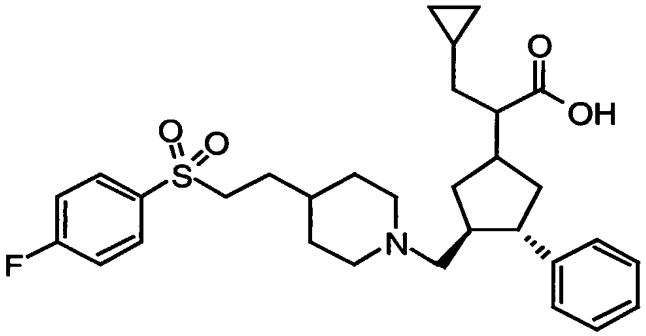
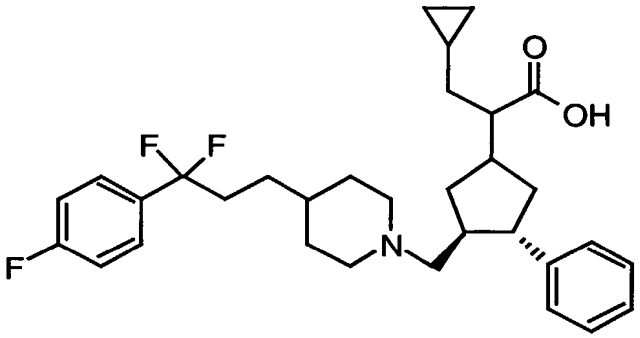




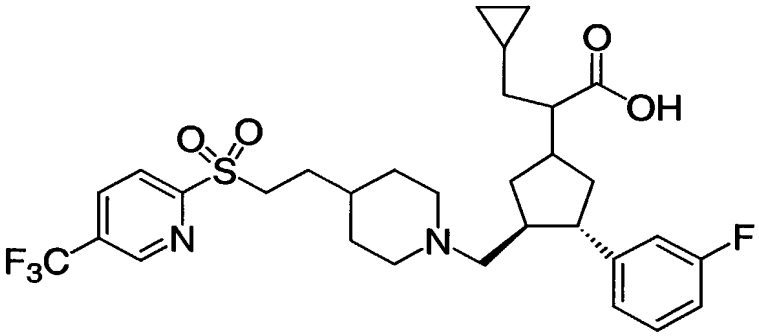


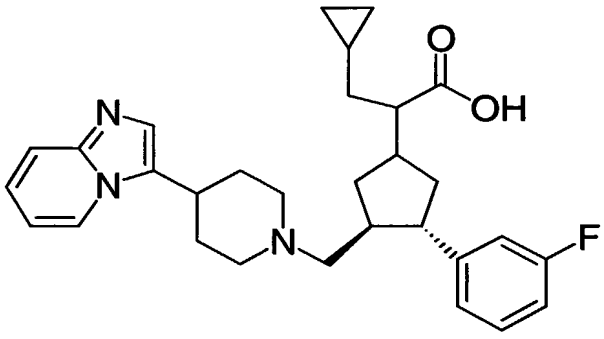


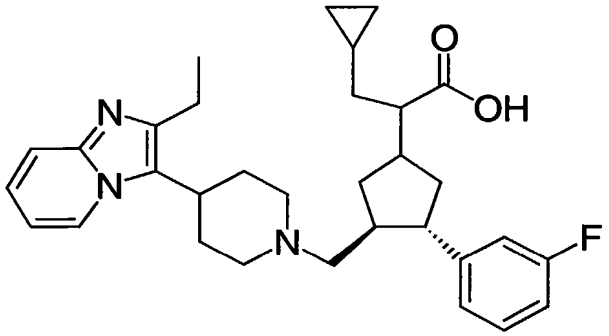


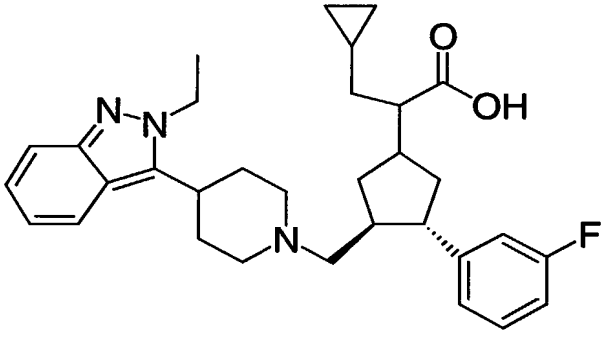
and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

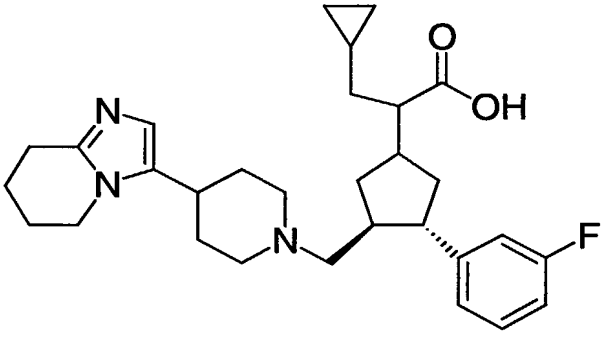
20. A compound of Claim 1, which is a compound selected from the group consisting of:











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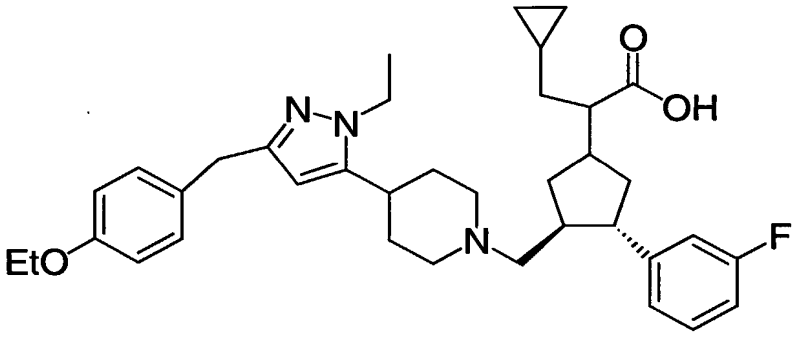

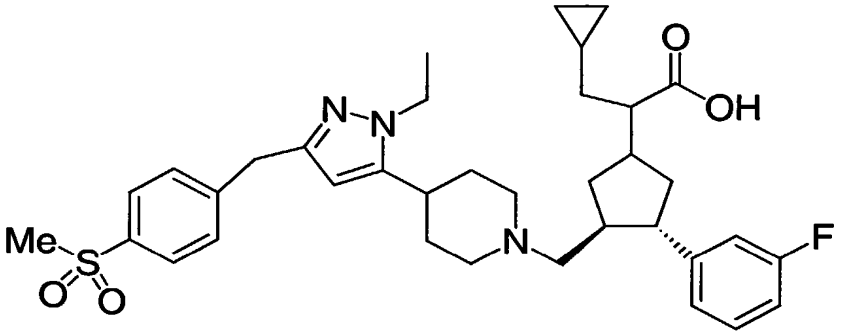

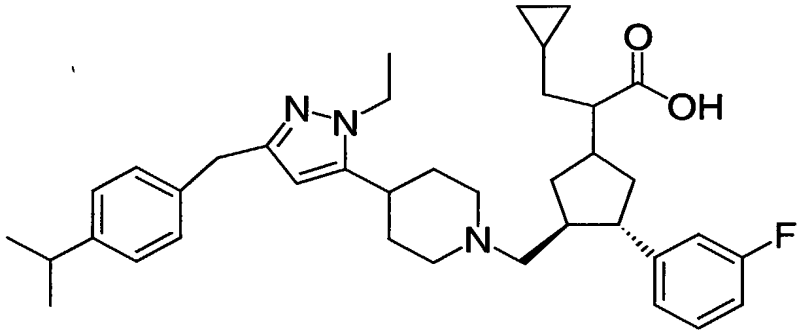

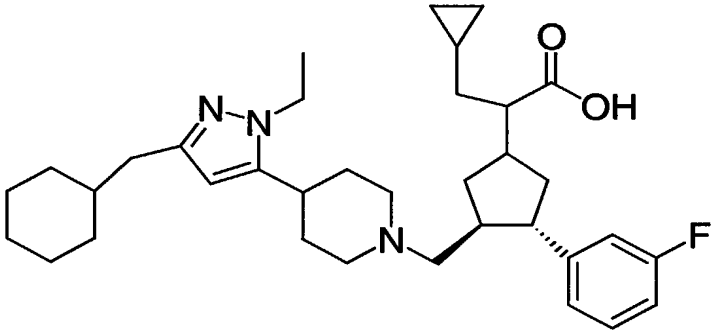

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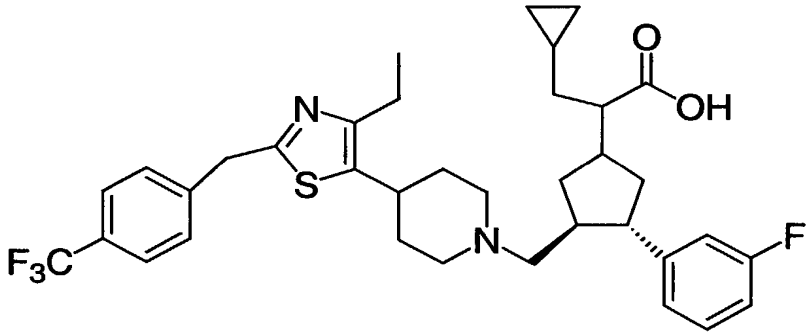
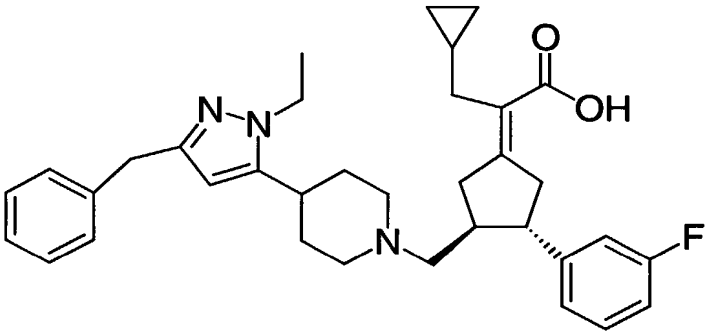
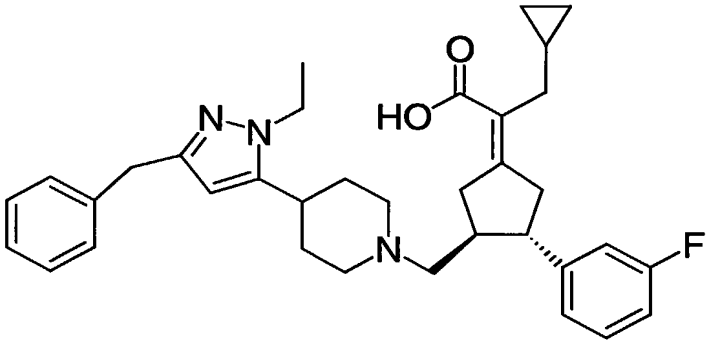
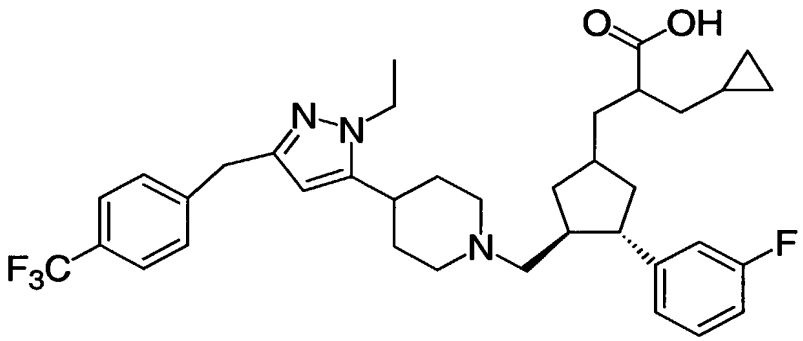


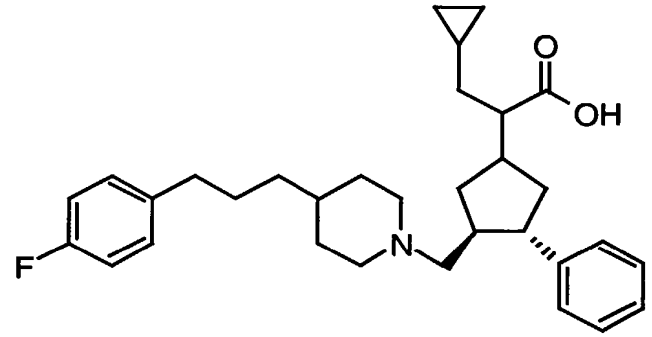


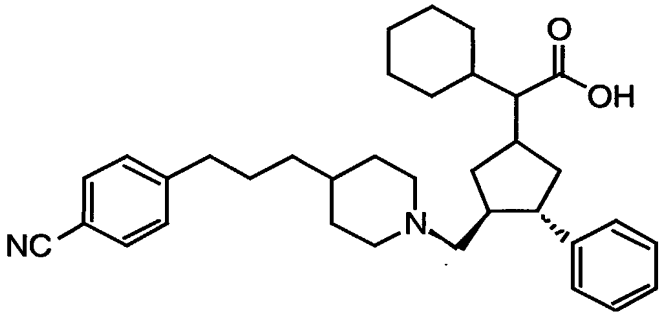


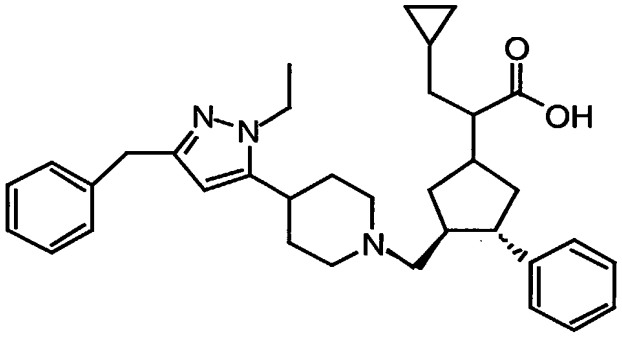


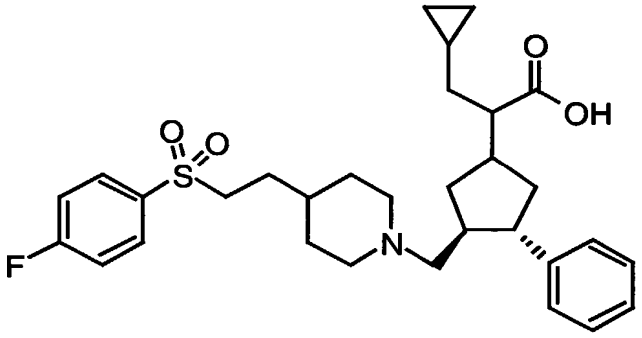
and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

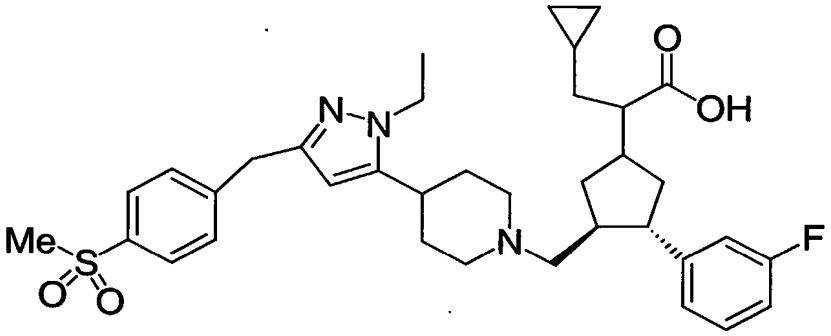
21. A compound of Claim 1, which is a compound selected from the group consisting of

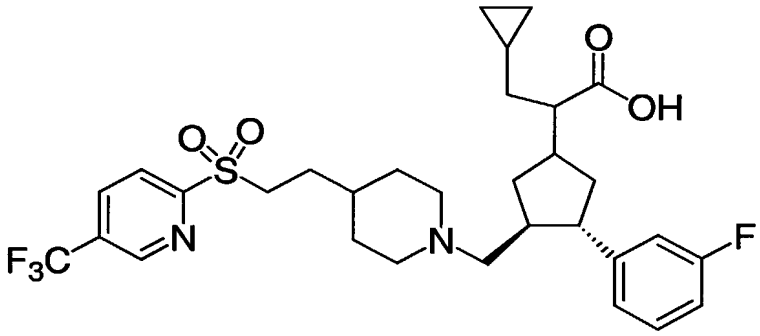


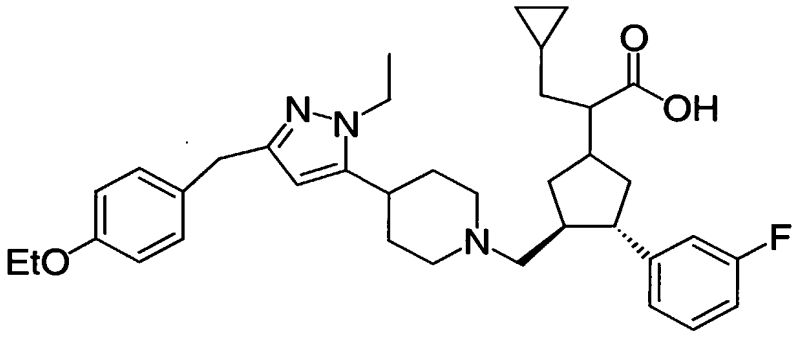


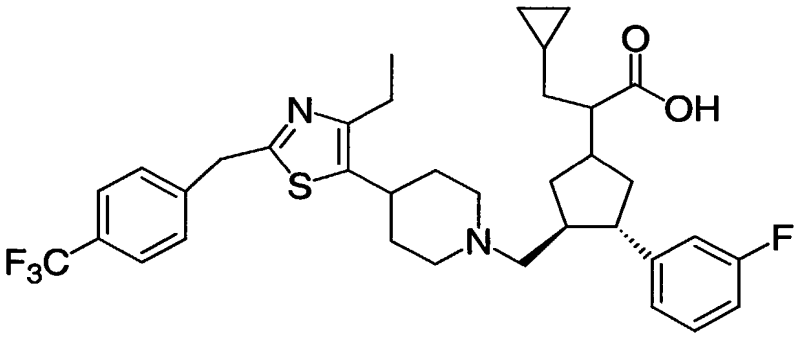


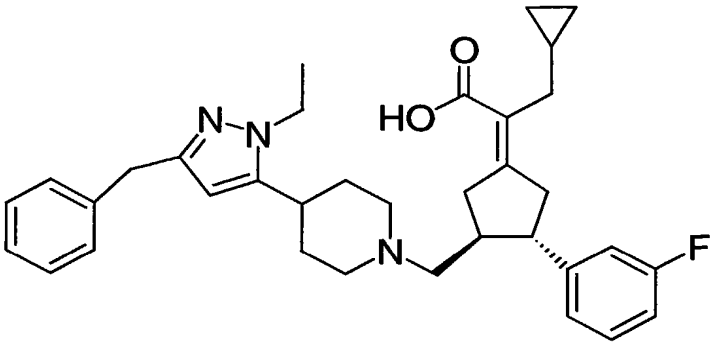


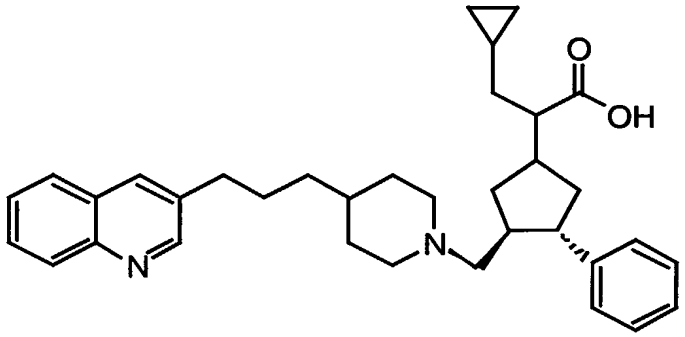












and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

22. A pharmaceutical composition which comprises an inert carrier and a compound of Claim 1.

23. A method for modulation of chemokine receptor activity in a mammal which comprises the administration of an effective amount of the compound of Claim 1.

24. A method for preventing infection by HIV, treating infection by HIV, delaying of the onset of AIDS, or treating AIDS comprising the administration to a patient of an effective amount of the compound of Claim 1.

25. A method for the prevention or treatment of an inflammatory and immunoregulatory disorder or disease which comprises the administration to a patient of an effective amount of the compound of Claim 1.

26. A method for the prevention or treatment of asthma, allergic rhinitis, dermatitis, conjunctivitis, atherosclerosis or rheumatoid arthritis which comprises the administration to a patient of an effective amount of the compound of Claim 1.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/15769

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) :IPC7 A61K 31/445; C07D 211/06; 215/12, 14; 401/08
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/311, 317, 319, 322, 326, 331; 546/174, 199, 205, 209, 210, 211

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS--structure
EAST/WEST--chemokine receptor

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, 3,647,804, A1, (RYNBRANDT ET AL) 07 March 1972, see entire document, especially esamples 34-42.	1-21
A	US, 5,750,549, A1, (CALDWELL ET AL.) 12 May 1998, see entire document.	1-26
A, P	Database CAS on STN (Columbus, Ohio, USA) abstract No. 133:43441,Preparation of N-ureidoalkyl-piperdines as modulators of chemokline receptor activity., , see entire article.	1-26

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search
15 AUGUST 2000

Date of mailing of the international search report
21 SEP 2000

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/15769

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

514/311, 317, 319, 322, 326, 331; 546/174, 199, 205, 209, 210, 211